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PAGET'S DISEASE OF THE FEMALE BREAST

WITH SPECIAL CONSIDERATION OF BIOPSY AND PREOPERATIVE IRRADIATION

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Paget concluded from his observation of fifteen patients, each of whom presented a raw, finely granular nipple or an acute diffuse eczema of the nipple followed in one or two years by cancer of the breast, that chronic conditions of the skin of the nipple and areola are often succeeded by carcinoma of the mammary gland. He suggested and carried out excision of the involved area of the nipple and areola, but, as he himself acknowledged, too late.[1] This conclusion of Paget that the primary lesion was on the nipple and areola and that the tumor of the breast was secondary was debated in the surgical literature from 1874 until 1924, a period of forty-eight years. And Kilgore,[2] as late as 1921, after studying the material in the laboratory of surgical pathology of the Johns Hopkins Hospital, felt that while Paget's disease is usually primary in the nipple, in rare instances the lesion may be secondary to cancer of the breast.

This debate is not to be continued here, but I wish simply to state that the cases on which this study is based consist only of those in which the primary lesion was on the nipple or areola. At the same time I recognize that ulceration of the nipple occurs not infrequently in cases of advanced cancer of the breast associated with retraction of the nipple.

At the beginning of his studies on Paget's disease in 1907, Bloodgood[3] favored Schambacher's view that the changes in the nipple and skin are secondary to the tumor of the breast. This opinion was based on the observation of cases of the advanced stage only, because in 1922, he wrote: "In the first 20 years of my experience I observed

1. Paget, James: St. Barth. Hosp. Rep. **10**:87, 1874.

2. Kilgore, Olson R.: Is Paget's Disease of the Nipple Primary or Secondary to Cancer of the Underlying Breast? Arch. Surg. **3**:324 (Sept.) 1921.

3. Bloodgood, J. C., in Kelly, H. A., and Noble, C. P.: Gynecology and Abdominal Surgery, Philadelphia, W. B. Saunders Company, 1907.

Paget's disease only in the late stage. I always subjected it to the complete operation. None were cured."

The emphasis of the modern conception of Paget's disease dates from Bloodgood's [4] article in 1924, when he presented the evidence for and the conclusion that Paget's disease of the female nipple may be a preventable disease and curable in its early stages. The evidence that Paget's disease of the nipple may be a preventable disease was based on the observation of two cases of red, granular nipple and six cases in which there was a wart on the nipple, which healed under cleansing and protective measures.

The evidence for the conclusion that Paget's disease is largely curable in the early stages was obtained from twenty cases in which operation was performed. In seven of these cases of red, granular nipple, wart and superficial ulcers, the lesion was proved on microscopic study to be benign. In nine, microscopic study revealed cancer without involvement of the axillary glands. The condition in the remaining three cases was advanced, with metastasis to the axillary glands, and belongs to the group originally described by Paget—an ulcer of the nipple, a mass in the breast and palpable axillary glands.

In one case the nipple only was removed, and cancer was overlooked in the sections. Two years later the complete operation was performed, and cancer was found in the breast and axillary glands. The patient died of cerebral metastasis one year later. This case demonstrates the danger of incomplete operation.

Paget's cancer of the nipple is comparatively uncommon. In the surgical pathologic laboratory of the Johns Hopkins Hospital, until 1924, it had been observed only twelve times in about three thousand lesions of the breast, an incidence of less than 0.5 per cent. There has been no report on Paget's disease of the nipple from the clinic of the late Dr. Bloodgood and his associates since Bloodgood's report in 1924. My intention is to present the results of additional experience since that time and especially to report on what seems to have been a remarkable, if not unique, opportunity, of observing five cases of Paget's cancer of the nipple in the last two years. From the facts brought out by the study of this new material, the following conclusions seem justified.

1. There may be no difference clinically between a small, apparently insignificant lesion of the nipple which is benign and one which under the microscope shows fully developed Paget's carcinoma. When such a lesion does not heal in a few weeks by simple cleansing and protective measures, a biopsy should be performed.

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4. Bloodgood, J. C.: Paget's Disease of the Female Nipple: A Preventable Disease, Curable in Its Early Stages; a Study of Thirty Cases, Arch. Surg. **8**:461 (March) 1924.

2. The biopsy for a lesion on the nipple should consist of complete excision of the nipple, the areola and the central zone of the breast beneath.

3. Fully developed cancer of the nipple may be present without the presence of a fissure or an ulcer. There may be only slight keratosis surrounded by an area of irritation, the entire apparently innocent lesion being confined to the nipple only.

4. When microscopic study of the sections made from the tissue removed for biopsy shows Paget's carcinoma, operation for complete removal of the breast should follow.

5. There is apparently no danger in delaying the complete operation after biopsy of the type described in order to carry out thorough preoperative irradiation of the supraclavicular area, axilla and breast.

6. When an ulcer on the nipple is associated with a palpable mass in the breast or with palpable axillary glands, there is no danger in delaying the complete operation for one course of preoperative irradiation. There is nothing to be gained by biopsy in such cases.

7. There seems to be a distinct danger in irradiation of an apparently insignificant lesion of the nipple without performing a biopsy previously, unless this irradiation is to be followed by a complete operation, because an ulcer which is the seat of cancer may heal over entirely under irradiation, leaving the cancer in the breast and the axillary glands unobserved. There is one exception to this statement, which will be noted later.

8. The restriction of the operation to the excision of the nipple, areola and central zone of the breast beneath is justified only on the basis of expert pathologic knowledge, and if there is doubt as to whether the lesion is malignant while the sections are being submitted for the opinion of others, there should be irradiation.

9. Sufficient time has not elapsed to allow any conclusion as to the increase, if any, in the percentage of cures by the addition of preoperative irradiation, but sufficient evidence has accumulated to allow me to say that there is apparently no danger in delaying the complete operation for preoperative irradiation.

BENIGN LESIONS OF THE NIPPLE

From 1925 to 1935, inclusive, there were examined in this clinic fifty-eight patients with lesions of the nipple or areola, and of these, forty-nine had benign and nine malignant lesions (table 1). Sixteen of the forty-nine with benign lesions were subjected to operation, and thirty-three were not (table 2). Before taking up the nine cases of cancer of the nipple, I want to consider the benign lesions in some detail. In the group of thirty-three patients who were not operated on there were twenty-four with uncomplicated keratosis of the nipple which healed

quickly when simple cleansing and protective measures were employed. There was one patient whose nipples were sore, but there was no keratosis or other apparent lesion, and the soreness disappeared after the institution of treatment such as is given for keratosis. In three instances the keratosis of the nipple was complicated by the presence of a superficial ulcer or a small fissure, and in these three instances there was complete healing.

The condition in these three cases did not differ clinically in any respect from that in the four in which the nipple and areola were excised for diagnosis, except that the lesion healed quickly under treatment with soap and water, alcohol and petrolatum. Twice warts on

TABLE 1.—*Incidence of Lesions of the Female Nipple (1925 to 1935, Inclusive)*

Type of Lesion		No. of Cases
Benign lesions		49
No operation	33	
Operation	16	
Malignant lesions		9
Clinically malignant	4	
Clinically questionable	5	

TABLE 2.—*Incidence of Operation for Benign Lesions of the Female Nipple (1925 to 1935, Inclusive)*

Condition		No. of Cases
No operation		33
Uncomplicated keratosis	24	
Sore nipples, no keratosis	1	
Keratosis and superficial ulcer or small fissure	3	
Warts	3	
Papilloma of areola	2	
Operation		16
Keratosis and ulcer or fissure or red granular nipple	4	
Retraction of nipple with wart or red granular nipple	7	
Benign adenoma of nipple	2	
Infected dermoid cyst of areola	1	
Fibroma of areola	2	

the nipple were observed to heal under the same cleansing and protective measures. In these instances the warts were confined to one nipple. In another case a wart occurred on each nipple.

A woman 21 years of age was first seen at the clinic on Feb. 20, 1933. There was a diffuse wart on each nipple associated with congenital retraction of the nipple. The condition had been present for five years. Under cleansing and protective measures there was distinct improvement during the subsequent four weeks that the patient was observed. She was then lost from observation until Nov. 27, 1935, when she returned as a result of the follow-up card. The warts were just as distinct as when I first examined her in February 1933, two years and nine months before. As she had neglected the treatment prescribed during this interval, it was tried again for two months, and as there was no improvement the patient

was referred to Dr. Neill for radium treatment on Jan. 23, 1936. The examination on March 25 showed marked improvement in the warty condition of both nipples, but the warts have not yet completely disappeared.

The irradiation in this case for an apparently benign lesion was given because of the age of the patient and the bilateral involvement.

In the remaining two cases in which operation was not performed papilloma of the areola was present, which apparently is not an etiologic factor in cancer of the nipple and areola.

Of the sixteen cases in which at operation the lesion was diagnosed as benign in the frozen section, there were four in which keratosis

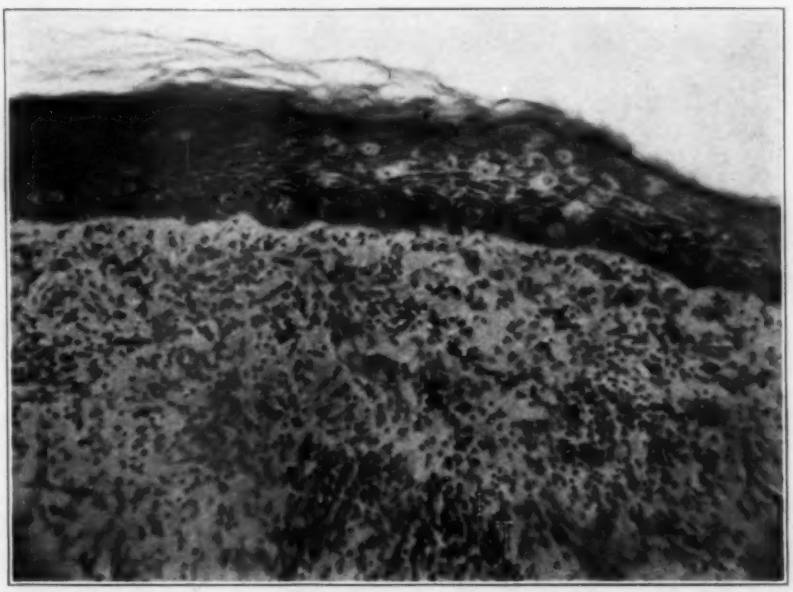

Fig. 1.—Low power photomicrograph of a section through a nipple showing Paget's carcinoma. This case is the earliest example of this condition at the clinic. Excision of the nipple and areola was done on Jan. 13, 1926. Complete operation for cancer was performed two years later. Death occurred five and one-half years after excision of the nipple, from metastasis.

was combined with an ulcer, a fissure or a red, granular nipple and the lesion failed to heal under treatment, and yet microscopic study in three still showed a benign ulcer. Irradiation was not done in these three cases, and no operation other than the excision of the nipple, areola and central zone of the breast was performed. There has not been a recurrence in any of the cases.

The lesion in the fourth case was also diagnosed as benign, but it has been reported that the patient died five and one-half years later

from cancer of the same breast and that two years before death a complete operation had been performed.

A restudy of this case shows Paget's cancer in the sections taken for biopsy. It is the earliest example of Paget's carcinoma of the nipple at the clinic, and evidence would indicate that the patient would have been cured had the disease been recognized at the time of the biopsy and a complete operation performed (figs. 1 and 2).

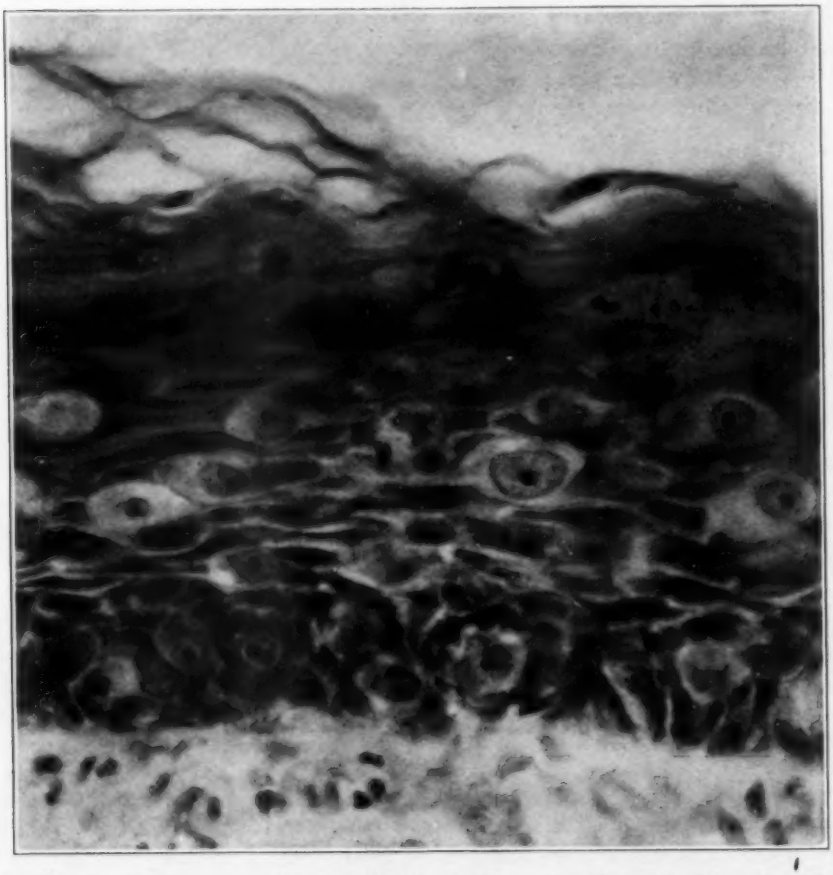

Fig. 2.—High power photomicrograph of the section shown in figure 1. The large cells are malignant although still confined to the epidermis.

There are seven cases in which there was retraction of the nipple, associated with a wart, an ulcer or a red, granular nipple, and in six instances the microscopic picture was distinctly benign. In one case there was a disagreement among those who studied the sections as to whether the lesion was malignant. This patient was given two courses

of irradiation but was not subjected to the complete operation, and she was well when last examined in September 1935, five months after operation.

In one instance a patient with cancer of the breast had a red, granular nipple on the opposite breast associated with a wart, and at the time of the operation on the cancerous breast I also excised the nipple which was the seat of the wart. This case must be eliminated from any study of the ultimate results, as the patient died in two years from cancer primary in the opposite breast.

There is one case in the group of instances of benign lesions in which operation was performed which I wish to report a little more in detail, because it was unique in my experience until 1927, when the patient came under observation.

Fig. 3.—Photograph showing a large nipple with a large benign adenoma beneath. The clinical diagnosis was Paget's cancer. Complete operation without exploration was performed on Oct. 18, 1927. There was no metastasis to the glands. The patient was well in February 1936. For the photomicrograph made in this case see figure 4.

Mrs. W., aged 40, the mother of four children, was examined by me on July 5, 1927. The examination revealed a very large, red nipple in which there were two sinuses. The red nipple was surrounded by a blue zone, and between the red and the blue zone there was a line of demarcation. This nipple was firm, hard and very tender. It had been in this condition for one month. At first there was a crust, and when the crust came away the two sinuses appeared (fig. 3).

In 1911, sixteen years prior to my examination, before the patient's marriage, Dr. Bloodgood had excised a benign papilloma of the nipple, and there is a note that at this time the nipple was harder and more prominent than the opposite nipple (left). When the patient nursed her first child she had a great deal of trouble with the right nipple, but if there was lactation mastitis there was no abscess, and there was less trouble during subsequent lactations.

She was given cleansing and protective treatment to the nipple, and disappeared from observation from July 5 to Oct. 13, 1927, during which period she was under the care of her family physician.

On Oct. 18, 1927, I performed a complete operation without biopsy or exploration. The glands were not involved, and there was no evidence of cancer in the nipple or in the breast. There was, however, a large benign adenoma just beneath the nipple, which could easily have been recognized in the gross and in the frozen section had I first excised the nipple and areola with a zone of the breast beneath (fig. 4). The patient is now well (January 1936), but she could have been saved the complete operation had I been familiar in 1927 with this type of benign adenoma of the nipple which presents the clinical appearance of Paget's cancer.

Fig. 4.—Low power photomicrograph of a section of the benign adenoma of the nipple shown in figure 3.

There is only one similar case in this series, and the patient is well more than eight years after excision of the nipple, areola and central zone of the breast only (figs. 5 and 6). Three other cases—infected dermoid cyst of the areola and two cases of fibroma of the areola—neither of any special significance in this study, complete the list of sixteen cases of benign lesions of the nipple and areola in which operation was performed.

Recently, a patient aged 53, in whom I excised the nipple, areola and central zone of the breast for retraction and irritation of the nipple of one year's duration, which on microscopic study proved to be benign, remarked: "If women only knew that when they had trouble

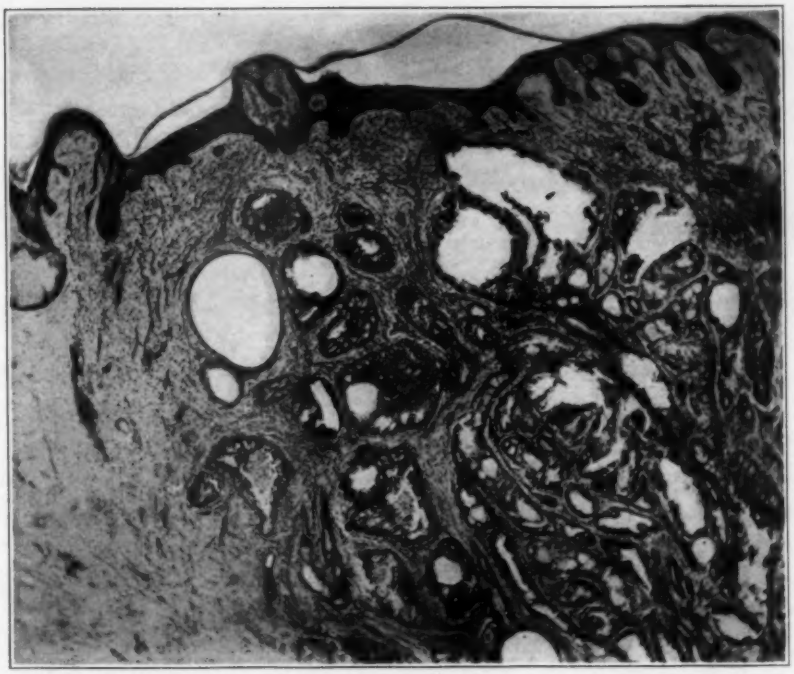

Fig. 5.—Low power photomicrograph of a section through the nipple in a case of benign adenoma of the nipple. Excision only of the nipple and areola and the central zone of the breast beneath was performed in September 1928. The patient was well in February 1936.

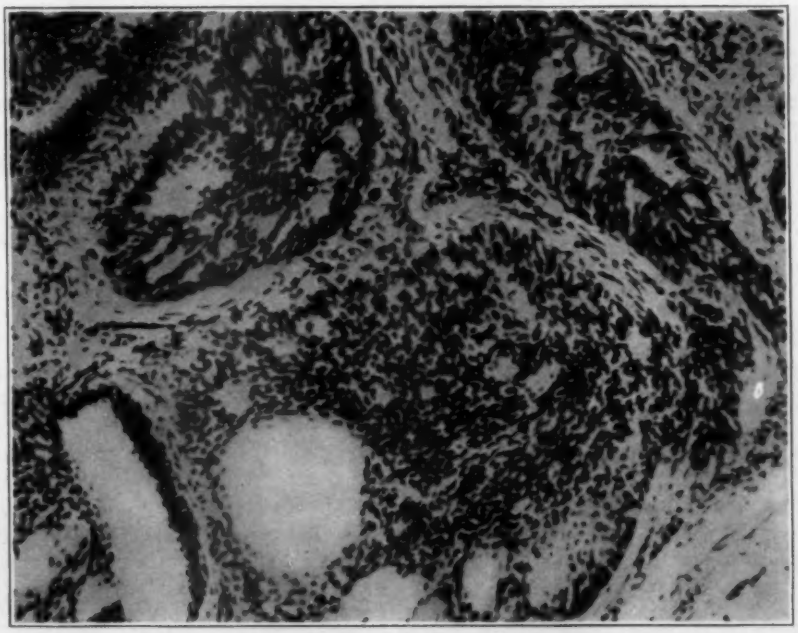

Fig. 6.—High power photomicrograph of the section shown in figure 5.

with the nipple they would not necessarily loose the entire breast they would consult their doctors sooner." This statement seems to be the secret of the prevention and cure of Paget's cancer of the nipple, and physicians must see to it that this statement is disseminated. It is my opinion that one is justified in even going a step further and stating that if women consult their physicians immediately when they notice something unusual on the nipple, or have an itching sensation on the nipple, the large majority not only will not loose the breast but will not even loose the nipple.

A study of the duration of symptoms in the group of cases of benign lesions in which operation was performed shows an average duration of symptoms of almost two years (twenty-two months). In the twenty-four cases of uncomplicated keratosis in which the operation was not advised, in the majority of instances the keratosis had not been noticed by the patient, but was found on examination. From this it seems that women are not quite as alert about an area of keratosis on the nipple as they are about a similar area on the skin of the face and that it might be a good plan for physicians to emphasize to women the importance of inspection of the nipples for keratosis and other lesions rather than to delay until symptoms appear.

PAGET'S CANCER OF THE NIPPLE

Of the nine cases of fully developed Paget's cancer of the nipple observed during the last eleven years, five have been observed during the last two years, and in this period there have been a total of three hundred and sixty-three cases of lesions of the breast, making the incidence of Paget's cancer in the past two years 1.3 per cent. In four of the nine cases the lesions were clinically malignant and in five clinically questionable. In the latter group the diagnosis was settled by biopsy. I wish to report these nine cases in detail.

Clinically Malignant Lesions.—Reports of the four cases in which the lesion was clinically malignant follow:

Mrs. S. E., aged 77, was seen at the clinic on Jan. 25, 1927. For from six to nine months there had been what she considered to be a fever blister on the lower part of the right nipple. There had been intermittent healing followed by recurrence and at times a little bleeding. A scab would form and fall off, leaving a red area exposed. Two months before she was seen she noticed a lump in the breast. The examination showed a small area of ulceration on the lower half of the nipple, with weeping, a palpable mass in the center of the breast larger than a silver dollar and palpable axillary glands. A roentgenogram of the chest showed no evidence of metastasis. On January 26 Dr. Bloodgood performed a complete operation, using local anesthesia. The sections from the nipple, the tumor in the breast and the axillary glands showed cancer (figs. 7 and 8).

Fig. 7.—Gross specimen from a complete operation performed by Dr. Bloodgood on Jan. 26, 1927. The photograph shows a small area of ulceration on the lower half of the nipple. Death occurred one year and five months after operation from an unknown cause.

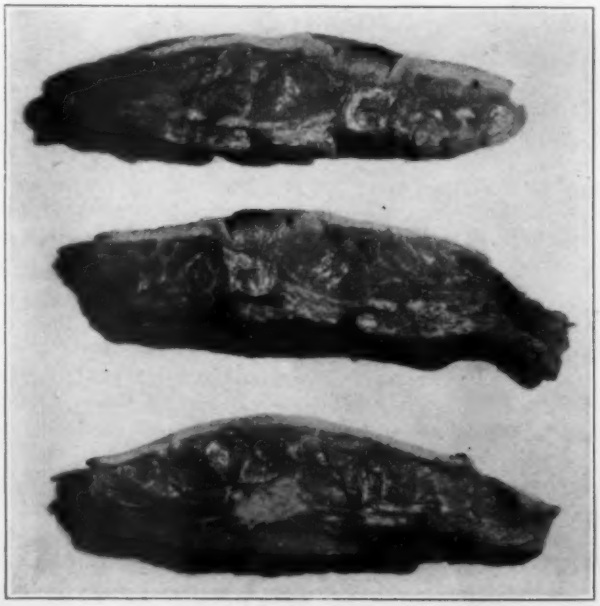

Fig. 8.—Gross section through the specimen shown in figure 7, showing gross cancer in the center of a fatty breast.

The patient died on June 15, 1928, one year and five months after operation. No accurate information as to the cause of death could be ascertained.

Mrs. M., aged 45, was seen on March 9, 1934. She was the mother of five children, the oldest of whom was 23 years of age and the youngest 7 years of age. She was menstruating normally. The left nipple was almost entirely destroyed, and surrounding the site of the nipple for an area the size of a 25 cent piece there was superficial ulceration and scabbing (fig. 9). There was no distinct mass just beneath the nipple, but in the midzone of the upper hemisphere of the breast there was a mass 6 cm. in diameter, over which the skin dimpled when the breast was raised forward. There was "pig skin" over the lower hemisphere of the breast, suggesting a lymphatic blockade; I was unable to palpate any glands in the axilla, but there was tenderness in the axilla on pressure. Transillumination of the breast showed a dark area at the site of the palpable mass in the upper hemisphere, but the breast beneath the nipple was clear (fig. 10).

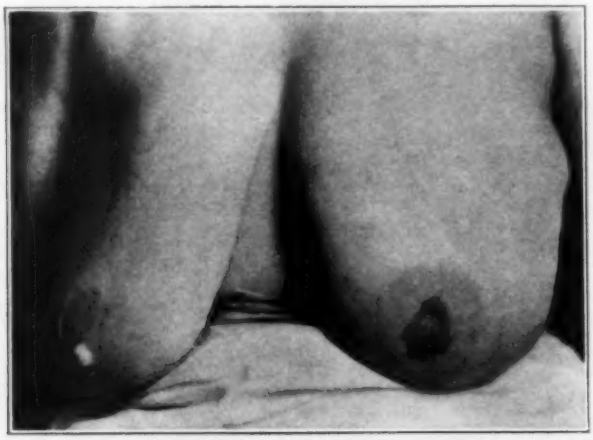

Fig. 9.—Photograph showing almost complete destruction of the left nipple with superficial ulceration and scabbing. Complete operation was performed on March 13, 1934, without preoperative irradiation. Death occurred on July 12, 1934, from metastasis.

Scabs had been present around the nipple for two years before examination, and although the patient sought medical advice at the onset and was given some local medicine, she did not again seek medical attention until one week before she entered the clinic. The mass in the breast had been present for one year, but the pig skin, which she called "goose skin," had been present only two weeks. Why I did not give preoperative irradiation I do not know, and there is no note that preoperative irradiation was ever discussed. In view of my experience now the patient should have been given the benefit of preoperative irradiation. I did the complete operation without biopsy on March 13, 1934, removing a large circular zone of skin about 16 cm. in diameter. There was metastasis to the base, middle and highest apex axillary glands and metastasis to the glands in the subscapular fossa. A roentgenogram of the chest taken on July 7, 1934, showed metastasis, and the patient died on July 12.

Mrs. M., the wife of a physician, was examined by Dr. Bloodgood and Dr. Stewart and myself on Jan. 2, 1935. She was 37 years of age and had one child, 9 years of age. Itching of the left nipple had been present for eleven months, and for ten months she had noticed a red area of irritation on the nipple (fig. 11). She and her husband had noticed a mass in the breast for six weeks.

On examination we found a crescent-shaped, red, granular area on the left nipple, subdued transillumination of the left breast and two palpable masses in the breast and a palpable gland in the base of the axilla. Roentgenograms of the

Fig. 10.—Photograph taken during transillumination of the breast shown in figure 9.

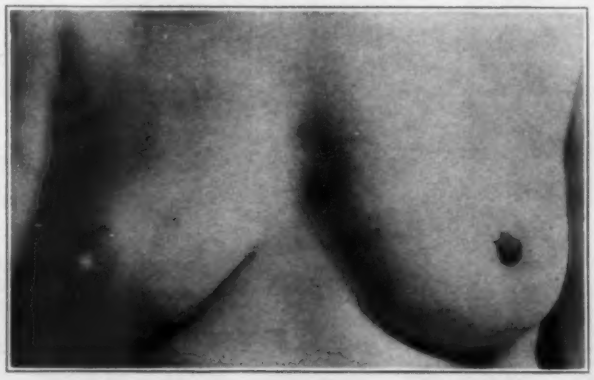

Fig. 11.—Photograph showing a red, granular left nipple.

chest, pelvis and skull showed no evidence of metastasis. Dr. Henry K. Pancoast, of Philadelphia, gave the preoperative irradiation, and on March 7 Dr. Floyd E. Keene, of Philadelphia, performed a complete operation. He found extensive metastasis to the axillary glands (figs. 12, 13, 14 and 15). After the operation there was further irradiation. Dr. Keene reported that the patient died on August 6, five months after operation, and that at autopsy there was extensive metastasis to the liver and peritoneum.

Miss L., aged 54, was referred to the clinic by Dr. Lillian E. Shaw, of Harrisburg, Pa., on Oct. 11, 1935. There was a scab on the right nipple, and

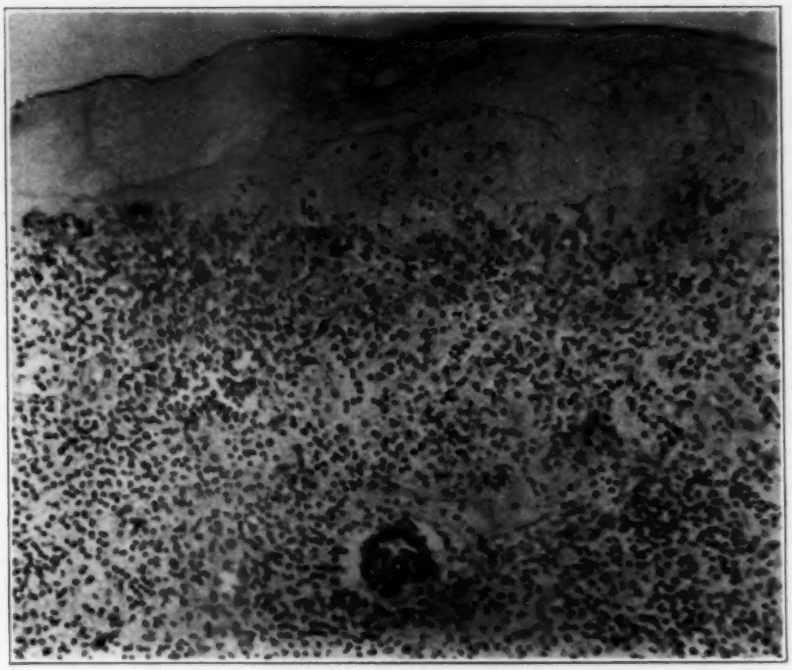

Fig. 12.—Low power photomicrograph of a section through the nipple shown in figure 11. A small nest of residual cancer buried in granulation tissue is seen.

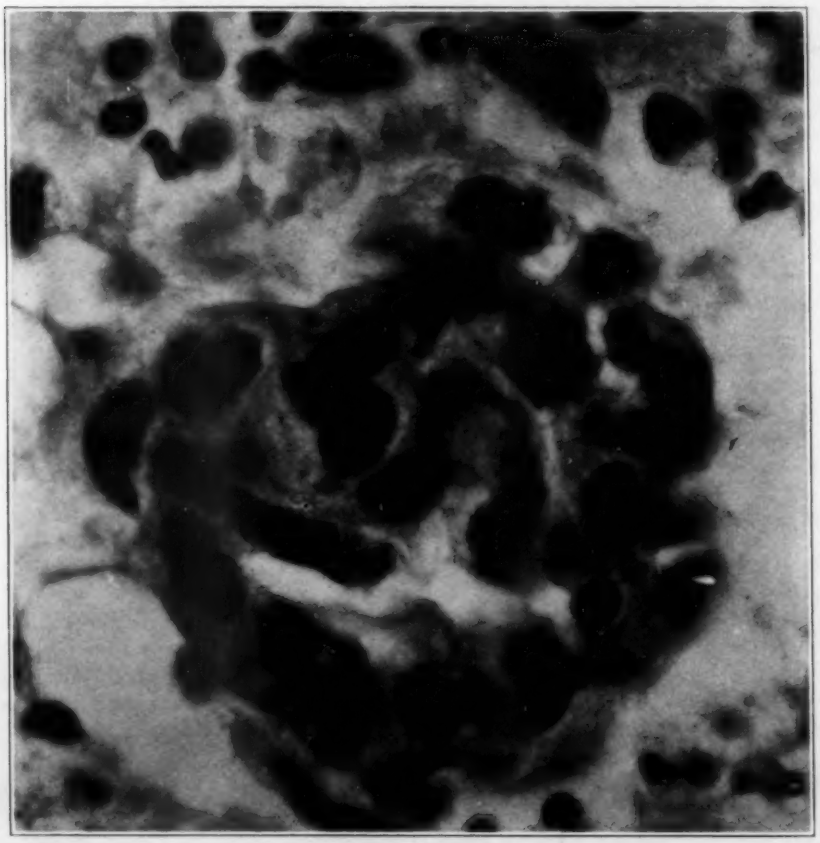

Fig. 13.—High power photomicrograph of an area of the cancer shown in figure 12.

the nipple had practically disappeared (fig. 16 *A*). On transillumination the right breast was a little darker than the left, and around the scab there was a little induration of the areola. There was also an area of induration in the upper, outer quadrant of the right breast about the size of a silver dollar, but there were no palpable glands in the axilla. A roentgenogram of the chest was normal.

One year before her coming to the clinic the patient's attention was called to the right nipple by itching, and the itching directed her attention to the presence of a crack on the nipple; later a crust formed on the crack. Although Dr. Shaw

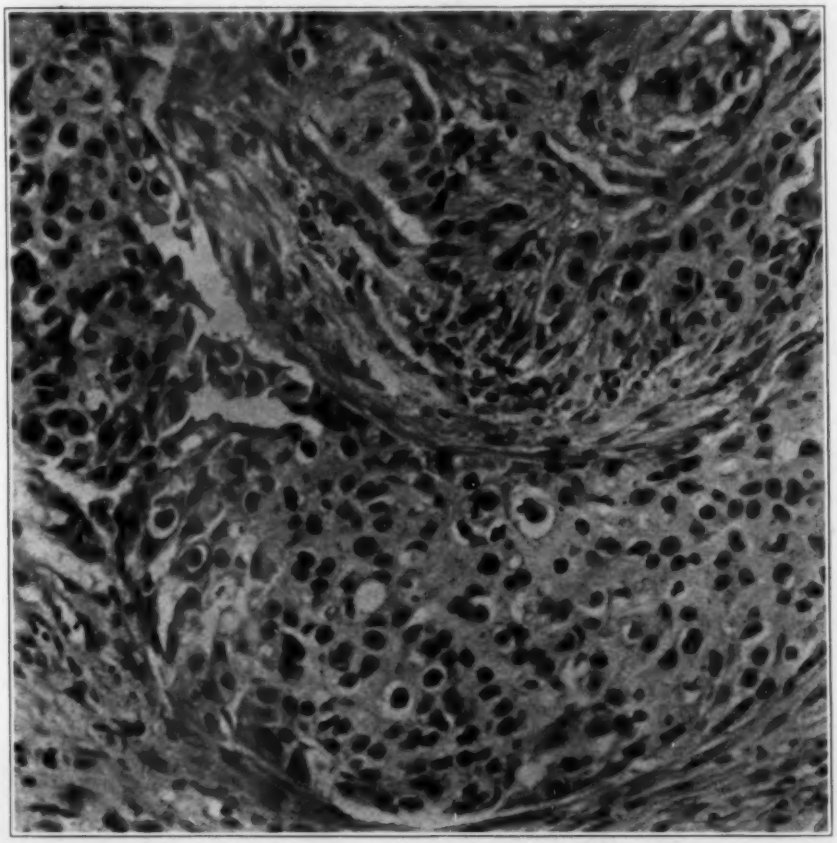

Fig. 14.—Low power photomicrograph of a section of the tumor of the breast shown in figures 12 and 13.

saw her and advised treatment a number of months before the present examination, she delayed because all sensations in the nipple disappeared and only a scab remained. In the fall of 1935 she noticed that the scab was a little larger, and for two weeks there had been pain in the breast, which had never been present before. I referred her to Dr. A. Z. Ritzman, of Harrisburg, for preoperative irradiation. She volunteered the information that during the first week of

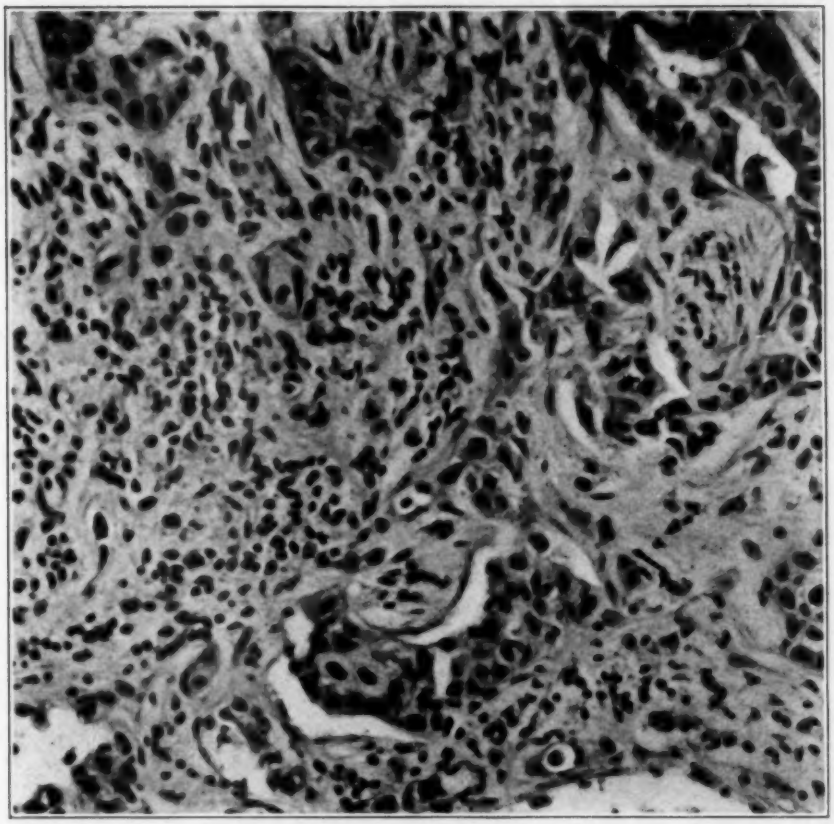

Fig. 15.—Photomicrograph of a gland from the axilla showing cancer. This photograph and figures 11, 12, 13 and 14 were made in the same case.

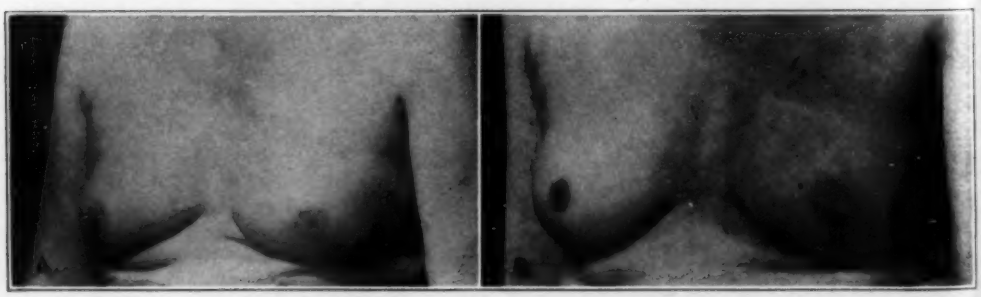

Fig. 16.—*A*, photograph showing a scab on the left nipple and destruction of the nipple. The photograph was taken before irradiation. *B*, a photograph taken after irradiation.

the irradiation the scab disappeared, leaving an open wound which discharged some material for about ten days.

When I examined her on November 16, one week after the irradiation was completed, there was epithelitis over the breast, axilla and supraclavicular area. There was no crust or ulcer on the nipple, but the areola was about twice the size of the opposite areola, with complete disappearance of the nipple. The site of the nipple was healed over completely (fig. 16*B*). There was still a distinct difference between the two breasts on transillumination and palpation.

I performed a complete operation on December 27. The section through the nipple at the site of the healed ulcer showed no evidence of carcinoma. Sections

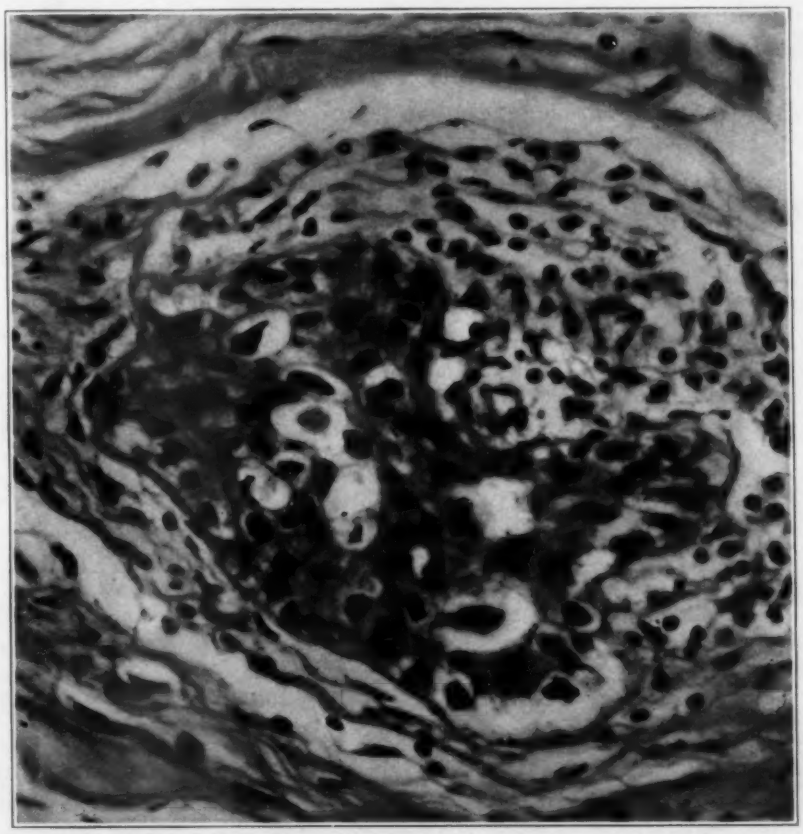

Fig. 17.—Low power photomicrograph of a group of cancer cells in the breast beneath the nipple after preoperative irradiation.

from the breast beneath the nipple showed distinct microscopic evidence of cancer, but only a few little islands of cancer surrounded by lymphoid cell granulation tissue (fig. 17). In another section through the breast at some distance from the nipple there was another small island of cancer.

Sections through the base, middle and highest apex axillary glands showed no metastasis. Dr. Gey was unable to grow the cancer cells in tissue culture.

Of these four patients who in addition to an ulcer of the nipple had a mass in the breast, three are dead, one year and five months, five months and five months, respectively, after operation. Judging from the tragic results in the three cases, the outlook in the fourth and very recent case would seem to be anything but hopeful. But I believe that the contrary is true and that as the axillary glands show no metastasis the patient's chances of remaining well and free from recurrence for five years are at least 70 per cent.

Of the three patients who are dead, one was given preoperative irradiation and two were not. As the chances of curing a patient with Paget's cancer of the nipple associated with a palpable mass in the breast by surgical measures alone are so small there seems to be no danger in the additional delay necessary for thorough preoperative irradiation (table 3).

Clinically Questionable Lesions.—It is the series of five cases in which the visible and palpable lesion was confined entirely to the nipple

TABLE 3.—*Results of Operation for Malignant Lesions of the Female Nipple (1925 to 1935, Inclusive)*

		No. of Cases
Clinically malignant lesions		4
Death from 4 to 17 months after operation with internal metastases	3	
Living and well (recent case, 12 months)	1	
Preoperative irradiation	2	
Clinically questionable malignant lesions		5
Death more than 5 years after operation, cause unknown	1	
Lost from observation	1	
Living and well from 1 to 5 years	3	
Preoperative irradiation	2	

without any clinical evidence of involvement of the breast or axilla which brings to light some interesting observations. In the first place, when the ultimate results in these five cases are compared with the ultimate results in the group of cases in which the lesion was clinically malignant, one finds an entirely different state of affairs. In the former five cases, three of the patients are living and free from recurrence for periods of five years, two years and one year since they came under observation. One patient was followed for five years, at which time she was free from recurrence, and then she was lost from observation. The fifth patient was well in June 1932, three and one-half years after operation, when last examined by her physician. Since this time she has been lost from observation.

It is evident even from such limited statistics that if any large percentage of patients with cancer of the nipple are to be cured they must be seen in the early stage and that both the patient and the phy-

Fig. 18.—Photograph showing a red, granular nipple with superficial fissure. Biopsy was followed by immediate complete operation on Aug. 15, 1927. Metastasis to the highest apex axillary gland occurred. No preoperative irradiation was given. The patient was well for five years and was then lost from observation.

Fig. 19.—Low power photomicrograph of a section through the nipple shown in figure 18. In spite of these early changes in the nipple and in spite of the fact that there was no palpable mass in the breast or microscopic evidence of cancer in the breast beyond the nipple zone, there was metastasis to the highest apex axillary gland.

sician must realize that the same attention should be paid to any irritation of the nipple in women who are not nursing children as in those who are.

On May 13, 1927, Mrs. B., aged 39, was seen at the clinic because of a watery oozing from the left nipple, of four months' duration. She was the mother of four children, the youngest of whom was 4 years of age. During the time she was nursing the child who was 6 years of age at the time of her admission to the clinic this same breast became sore and was very much enlarged and hard, and the nipple was sore. After she took the baby away from the breast for several days and applied some salve, the condition cleared. She put the baby back on the breast, and there was no further trouble until the onset of the present condition.

At the first examination there was a scab on the nipple, and this came away after the first application of petrolatum, leaving a superficial fissure on the nipple (fig. 18). Under treatments with soap and water, alcohol and petrolatum the nipple almost healed by June 9, a period of three and one-half weeks, and completely healed after the ulcer was treated with phenol followed by alcohol. However, the ulcer recurred in twelve days, and entirely healed for the second time by July 25, and recurred for the second time one week later.

In view of these recurrences of the ulcer, which was still only a minute superficial fissure, 3 mm. in diameter, I decided to operate. At the operation, on August 17, I excised the nipple and areola with the central zone of the breast beneath, using the endotherm needle. Frozen sections made immediately showed fully developed Paget's carcinoma, and after packing the wound with gauze wrung out of a 50 per cent solution of zinc chloride, I closed it hurriedly with silver wire and did a complete operation (figs. 19 and 20). The axillary glands were involved, and the section of the highest apex gland showed metastasis (fig. 21). No gross or microscopic cancer in the breast was observed beyond the microscopic involvement in the area of the nipple. Even though the patient's chances for remaining well and free from recurrence for five years were at most 10 per cent, she was living and well in 1932, after five years, and later was lost from observation.

When one considers that in this case there was a delay of more than three months between the first examination and the operation and that at operation cancer was found, with involvement of the glands, I feel that I postponed the operation for too long a period. I did this because the ulcer healed on two occasions. However, the ulcer did not heal under treatment with soap and water and alcohol and petrolatum alone, as phenol was added. I decided at this time never again to use phenol on an ulcer of the nipple, because there was definite proof that Paget's cancer of the nipple healed over under this treatment. I also decided at this time never to use radium or roentgen rays on the nipple, for I felt that this too might produce superficial healing. It was eight years before I had an opportunity to prove this. In the case of Miss L. this idea has been confirmed. Because of these two observations I believe that it is justifiable to state that there is a distinct

danger in masking the diagnosis if more than simple cleansing and protective measures are employed in an attempt to heal an ulcer on the nipple, no matter how superficial and apparently benign the ulcer appears. Definite proof of how long one is justified in using these simple measures before doing the biopsy has not been found, but an arbitrary time of three weeks is chosen. When the ulcer on the nipple is associated with a mass in the breast or with palpable

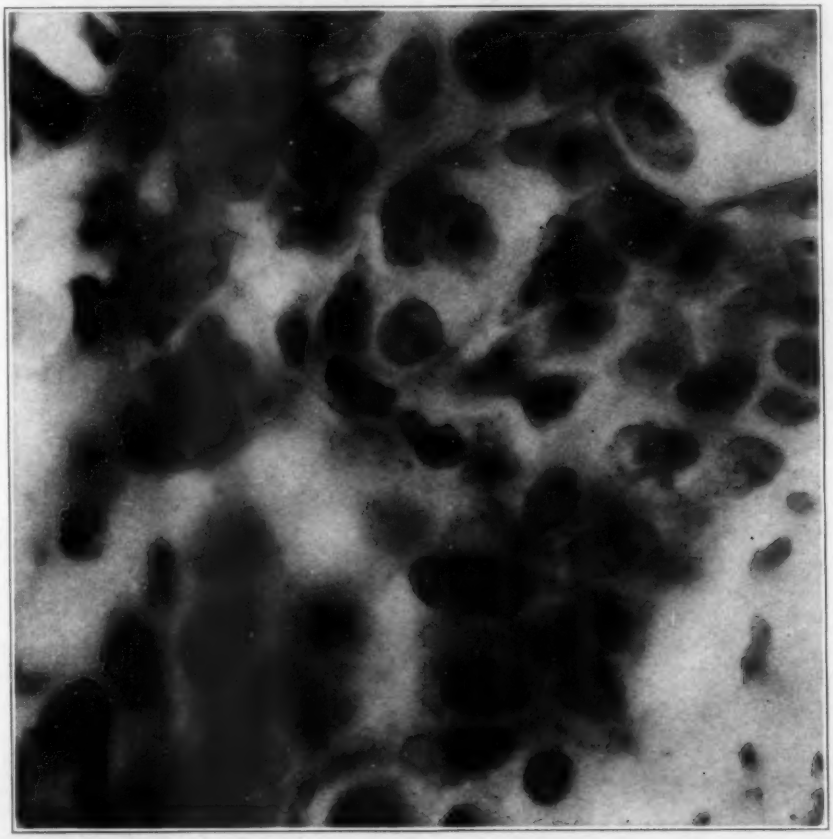

Fig. 20.—High power photomicrograph of an area of the section shown in figure 19.

axillary glands, preoperative irradiation is given, with the distinct understanding that the complete operation is to follow, regardless of whether or not the superficial ulcer heals.

The following case, that of Mrs. F., again demonstrates the danger of irradiation as a first treatment for a clinically benign lesion of the nipple.

A white woman, aged 55 was seen on Jan. 25, 1929, with the history of irritation of the nipple associated with a watery discharge from the nipple, both of which had been present for one year and nine months. She said at the beginning that the nipple had itched and that later it became scaly. She had consulted her surgeon in July 1928, six months previously, without telling him she had been given roentgen treatment to the nipple. Her surgeon prescribed a little petrolatum and cleanliness, and when he saw her one month later the nipple was

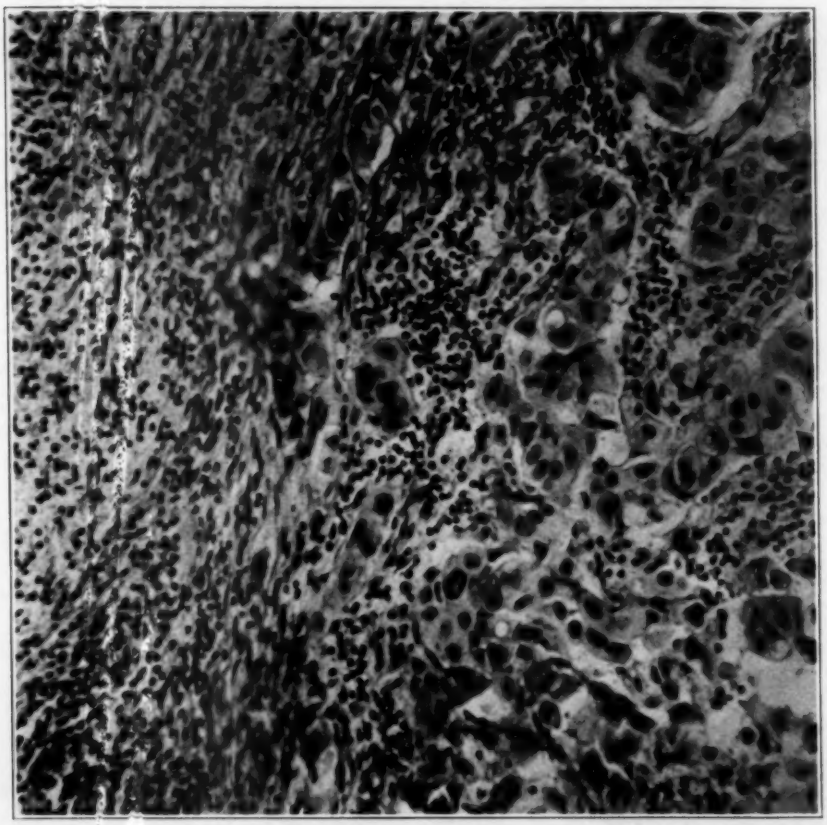

Fig. 21.—Photomicrograph of the highest apex axillary gland, taken in the same case as figures 18, 19 and 20.

normal, but when he examined her on Jan. 24, 1929, there was a line of nodules beneath the nipple and enlarged axillary glands, both of which were absent on his two previous examinations.

At the operation on February 1 Dr. Bloodgood excised the nipple and areola and the breast beneath, and as the frozen sections showed cancer he closed the wound and did a complete operation at once. Although the glands were palpable before operation, sections did not show metastasis. There was, however, cancer in the breast beneath the area excised at biopsy. The patient was well when

last examined by her physician in June 1932, three and one-half years after operation.

Mrs. R., aged 54, was first seen at the clinic on Sept. 24, 1930. She was the mother of three children, the oldest being 37 years of age and the youngest 21 years. The left nipple was of the red, granular type, with superficial ulceration of the nipple and areola. Transillumination of the breast was clear, and no mass could be made out in the breast or axilla on palpation. The left nipple had been retracted for thirty-seven years, dating from a caked breast at the time of the first lactation. One year before coming to the clinic the patient noticed a little secretion from the nipple and then a scab. Under the applications of zinc oxide ointment the scab has been appearing and disappearing. For three months, under some type of light treatment, the lesion dried up and then appeared again. On September 26, I made the usual biopsy, and as the frozen sections showed cancer, I followed this at once with a complete operation. There was no involvement of the breast beyond the zone of the nipple or of the axillary glands. The patient's daughter reported on Sept. 6, 1935, that her mother was well.

The following two cases, which will be reported in detail, are the two cases observed in the last two years in which the lesion was apparently confined to the nipple only, and in each case the nipple, the areola and the central zone of the breast beneath were excised for biopsy. In each case the sections showed Paget's cancer, and in each case preoperative irradiation to the breast, axilla and supraclavicular area was done, followed by a complete operation. In both instances residual cancer was found in the breast, but in neither instance was there metastasis to the axillary glands, nor did Dr. Gey obtain any growth of tumor cells in tissue cultures. These two patients are both well, but it is less than two years since the first one has been observed.

Mrs. B., aged 31, first came under observation on Jan. 5, 1934. The left nipple had been replaced by an ulcer, and on transillumination there was a dark area beneath the nipple the size of a 25 cent piece. The remainder of the breast was clear on transillumination, and there was no palpable mass in the breast or the axilla. Her one child was aged 15 years, and she remembers having a little trouble with this breast during lactation. In 1929, five years before coming under observation, there was acne of both breasts, which was not confined to the nipples but was all over the breast. She was given a salve for the acne, and after the acne disappeared there was itching and then a tiny crack on the left nipple. The crack became covered with a scab which would come and go. The patient went from 1929 to nine months before she came to the clinic before consulting a physician. When she consulted her physician because the nipple was sore she was given a powder and petrolatum to apply. Six months before her coming to the clinic another physician gave her a course of roentgen treatment, after which the ulcer would heal and then break down. In another clinic two months previously a small section was taken for biopsy and operation was advised.

On Jan. 5, 1934, the nipple, the areola and the central zone of the breast beneath were excised at the clinic. The sections showed Paget's cancer (fig. 22). The patient would not consent at this time to a complete operation. She was given irradiation at the Kelly Hospital under Dr. Neill. This was com-

pleted in February (fig. 23). She was observed frequently during February, March and April, and although there was no evidence of any remaining disease in the breast or axilla, Dr. Neill gave a second course of irradiation during the latter part of April and the first part of May. She was examined frequently

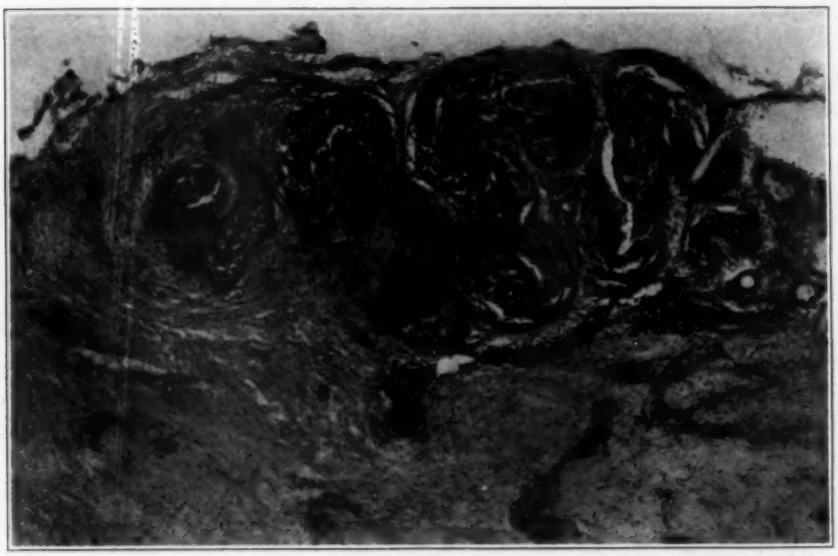

Fig. 22.—Low power photomicrograph of a section through the nipple, which was excised on Jan. 6, 1934. Fully developed Paget's cancer is shown.

Fig. 23.—Photograph taken on March 24, 1934, two months after biopsy, showing the extent of the excision. The microscopic section is shown in figure 22.

during June, July, September and November, and on Nov. 23, 1934, I excised a nodule smaller than a 10 cent piece, situated about 2.5 cm. below the scar of the biopsy. The gross and microscopic appearance was that of cancer. She allowed me to perform a complete operation on November 27. During the course

of the operation no grossly involved glands were encountered, and sections from the base, middle and highest apex axillary glands showed no evidence of metastasis. However, sections from the breast showed cancer, although Dr. Gey was unable to grow it in vitro.

In view of the fact that this patient would not consent to a complete operation at first and did not consent to it for ten months, there was no choice other than delay. The fact that even after this delay of ten months, during which two courses of irradiation were given, no metastasis to the axillary glands was found, is evidence that the delay was not harmful. The patient was last heard from on Jan. 3, 1936, at which time she was well.

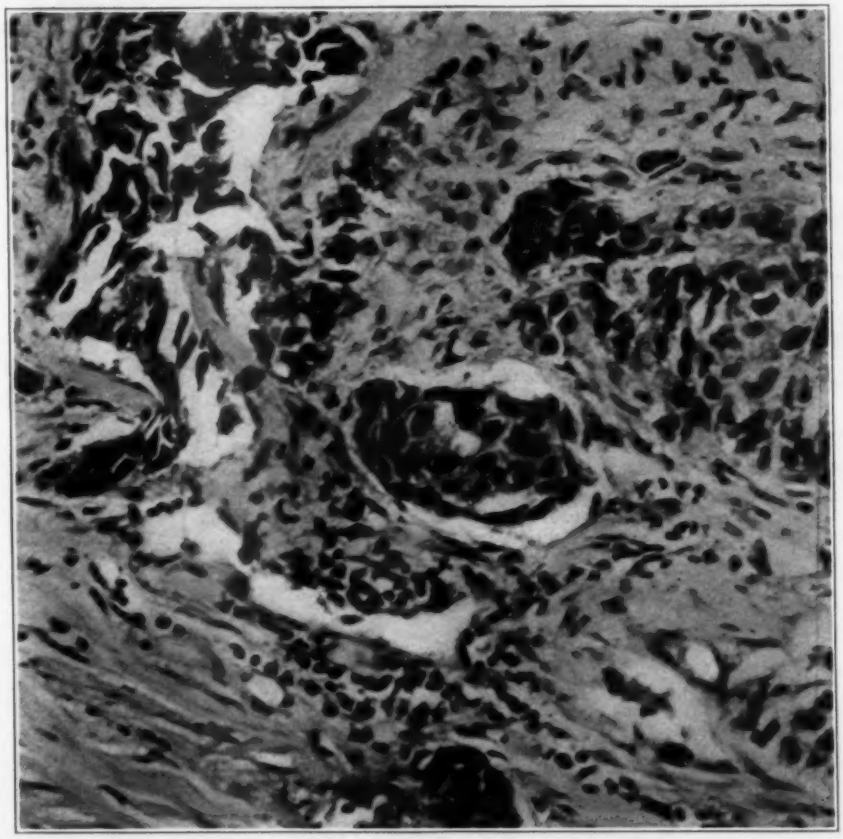

Fig. 24.—Photomicrograph showing residual cancer in the breast from a specimen removed at complete operation on Nov. 27, 1934, ten months after biopsy followed by two courses of preoperative irradiation.

One of the earliest and most interesting cases in this entire series is this last case, which presents an example of fully developed Paget's cancer of the nipple coming under observation before the stage of an ulcer.

Mrs. C., aged 46, came to the clinic on Dec. 11, 1934, because of a recurrent itching of the nipple of one year's duration and because a drop of blood had been observed recently. Examination showed an area of keratosis only 1 mm. in diameter, but there was a distinct difference in the appearance of the two nipples. The epidermis of the left nipple showed normal wrinkling, while on the right nipple the epidermis was tense, shiny and a little red, but there was no evidence of ulceration. No mass was palpable in the breast, and there were no palpable

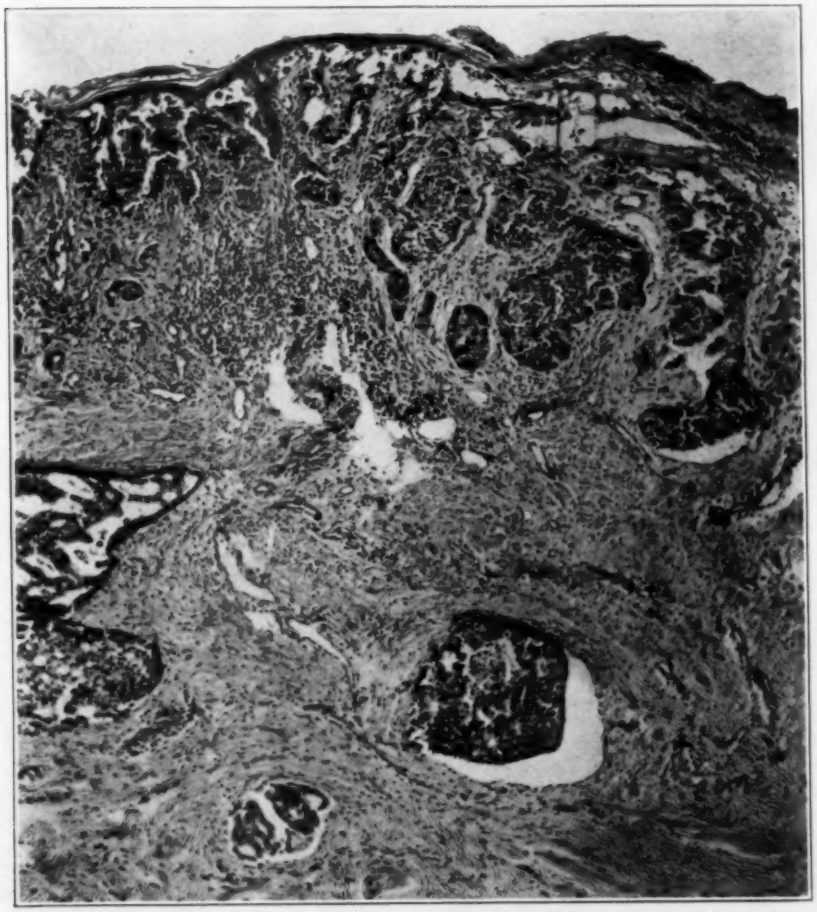

Fig. 25.—Low power photomicrograph of a section through the nipple from tissue removed for biopsy on Dec. 12, 1934, showing fully developed Paget's carcinoma.

axillary glands. Even after repeated attempts I was unable to demonstrate any difference between the two breasts on transillumination, even directly beneath the nipple.

The day of the first examination, December 12, I excised the nipple, the areola and the central zone of the breast, using procaine hydrochloride. The frozen

section through the nipple showed a very early but fully developed Paget carcinoma, and on Jan. 7, 1935, Dr. Gey reported a growth of the tumor in tissue culture (figs. 25 and 26).

Dr. Curtis F. Burnam, at the Kelly Hospital, began roentgen irradiation to the axilla on December 12 and subsequently carried the irradiation over the supra-

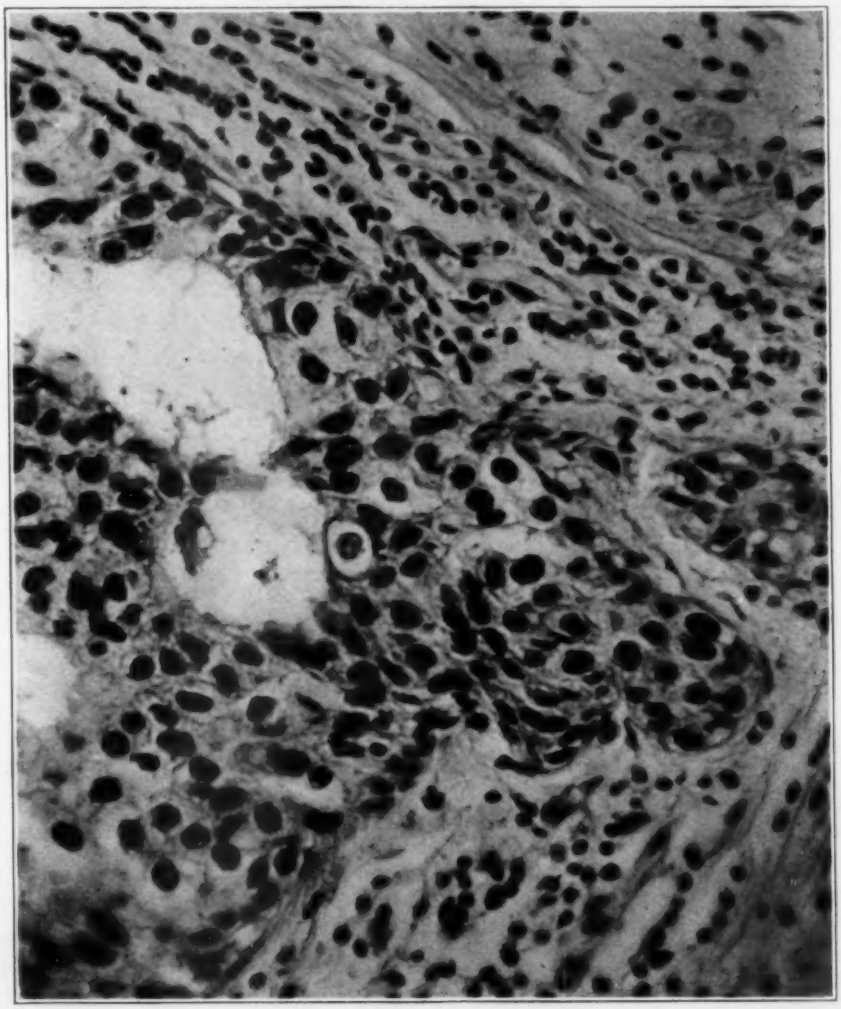

Fig. 26.—High power photomicrograph of an area of cancer beneath the nipple.

clavicular area and the breast. When the irradiation was complete the patient left for Florida, remaining until May. At the time of my examination, on May 16, 1935, there was no area in the breast suggesting recurrence, but there was a palpable gland the size of a 10 cent piece in the base of the axilla, although the following day I could not be quite certain about it.

Because there had been an interval of four months since the irradiation was completed, the patient was given a second course of irradiation from May 17, 1935, to June 15, 1935. On July 30, 1935, I performed a complete operation, and in the breast the only remaining evidence of cancer was a little nodule, the size of a pea, on the inner side of the scar. This nodule, however, had the gross appearance of cancer and was distinctly cancer histologically (fig. 27), but on August 13 Dr. Gey reported no growth in tissue culture. It will be recalled that this tumor grew in vitro before irradiation. There was no metastasis to the axillary glands. When the patient was last heard from, on March 15, 1936, there was no evidence of recurrence.

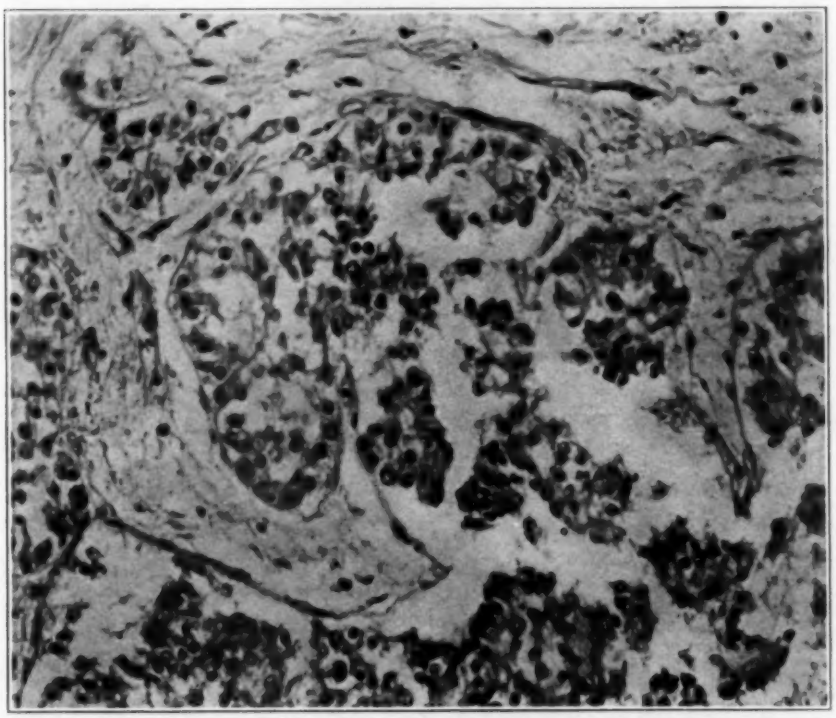

Fig. 27.—Low power photomicrograph of section taken through an area of residual cancer in the breast removed at complete operation on July 30, 1935, after two courses of preoperative irradiation.

In conclusion, I should like to refer particularly to two histologic pictures, that of the benign adenoma beneath the nipple and that of the very early stage of Paget's carcinoma of the nipple. (Compare figures 1 and 2 with figures 4, 5 and 6.) In the former lesion the structure of the overlying epidermis is either normal or changed by pressure of the underlying tumor, so that it is thinned out, and the papillary bodies are either lost or not pronounced. Beneath the epidermis there is a narrow zone of fibrous stroma infiltrated by cells of the fibro-

blast and plasma cell type. Beneath this narrow band of stroma is this nonencapsulated tumor composed of irregular lobules which coalesce so intimately that the limitations of the separate lobules are almost indistinguishable, and the borders of these lobules when they can be identified are identified by the narrow zones of intralobular stroma separating them. The ducts and acini composing these lobules show diffuse dilatation and hypertrophy and hyperplasia of the mucous membrane lining with the formation of folds, and the cells themselves are of the columnar epithelial cell type, quite different from the cell characteristic of Paget's carcinoma. There are cystic and solid areas in the tumor, and sometimes stellate areas like those in basal cell carcinoma, and when these stellate basal cell areas are present the condition is more likely to be confused with carcinoma. It is important to note that in the benign adenoma beneath the nipple the basal cell layer of the epidermis is intact even though the papillary body may be flattened out.

In Paget's cancer, on the other hand, the first change is in the morphology of the spinal cells in the epidermis. The next change is the loss of the basal cell layer of the epidermis, and spinal cells are seen in contact with the stroma beneath. Paget's cancer of the nipple is a spinal cell carcinoma arising in the spinal cell layers of the epidermis, and in the earliest stages it can be recognized not only by the loss in the basal cell layer mentioned but by the tremendous enlargement in the size of the spinal cells taking part in the process and the marked changes in the morphology of these cells. Frequently these larger cells can be seen in the various stages of mitotic division and are so characteristic in appearance that they are sometimes given the name Paget cells, although Paget never described this disease histologically.

PEPTIC ULCERATION

THE RELATIVE PROTECTIVE VALUE OF THE ALKALINE DUODENAL JUICES

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Few subjects in medicine have received the perennial inquiry and the indomitable resoluteness of the clinical and experimental investigator that has the subject of peptic ulceration. This is evinced by the profound and voluminous literature amassed in the comparatively short period of approximately seventy-five years. This indubitable statement in itself is clearly indicative of the ineluctable conclusion that although much has been learned there is still little definitely known concerning the etiology of the disease. The multifarious hypotheses, the diversity of opinion and the eagerly challenged statements clearly reveal the perplexing problems of its causation.

No other condition has more provokingly incited the workers of the various special fields of medicine. The interest of the anatomist is aroused by the possible relationship of the blood and nerve supply to the characteristic location of the ulcer. The pathologist is attracted by its typical occurrence and its relationship to carcinoma. The presence of infection has instigated the bacteriologist to study the disease. The relationship of the digestive juices has actuated the physiologist toward its investigation. Its importance to the roentgenologist is manifest by its addition to his vainglorious list of accurately diagnosable conditions. The clinician is inspirited by the sad realization of the inadequacy of the purely medical measures as a complete cure. Finally, the surgeon is particularly interested, because he is always considered as the last resort and because he is offered an unusual opportunity to display his ingenuity in devising varied and more suitable operative procedures. These specialized interests and investigations undoubtedly have been to some extent conducive to the existing maze of confusion, bewilderment and contradiction. Each worker in his specialized field, viewing only his tessera in the mosaic, becomes prejudiced in his conception, allegorically recalling the six blind men and the elephant.

As a result, there are now no less than twelve theories and hypotheses, all of which emphasize certain factors which undoubtedly play

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some rôle in the etiology and pathogenesis of the disease. As these theories have been admirably reviewed in previous publications,[1] it will be superfluous as well as irrelevant to attempt their detailed discussion here. However, because of its appositeness in this particular investigation, it is considered pertinent as well as essential to give an account of the development of the chemical theory.

The chemical theory is the result of the accumulation of certain clinical and experimental observations. This strictly limited localization of the occurrence of ulcer with striking uniformity cannot be regarded as coincidental but must have a satisfactory explanation. The occurrence of ulceration in only those areas which are habitually bathed in acid chyme and in other parts of the intestinal tract only under exceptional circumstances which permit exposure to the gastric secretion has indicated the culpability of the acid gastric juice. On the basis of this reasoning, it has been concluded that there occurs insufficient neutralization or some abnormal inability of the alkaline duodenal juices to neutralize the normal or probably hyperacid gastric secretion. Investigators throughout the world have been stimulated to produce experimental evidence to substantiate this or to demonstrate some factor which might be totally absent, abnormally increased or abnormally diminished.

These studies have been directed in the main toward some method of approach by which the influence of the alkaline duodenal contents could be determined. A review of the diversified procedures and their modifications is a study in ingenuity, although the underlying principle remains the same. The purpose of the majority of the procedures has been to determine the relative values of the alkaline juices alone and in combination with each other. However, it was first necessary to devise some method by which ulcer could be produced in the dog, because it lends itself so well to experimental study and is particularly applicable to the study of ulceration, which so rarely occurs normally in this animal. That spontaneous chronic ulcer rarely occurs in the dog has been shown by Ivy [2] who did not find ulceration in eight hundred and fifty healthy

1. (*a*) Durante, L.: The Trophic Element in the Origin of Gastric Ulcer, Surg., Gynec. & Obst. **22**:399, 1916. (*b*) Greggio, Ettore: Des ulcères gastro-duodenoux, Arch. de méd. exper. et d'anat. path. **27**:533, 1916-1917. (*c*) Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920. (*d*) Hurst, A. F.: Pathogenesis of Gastric and Duodenal Ulcer, Guy's Hosp. Rep. **74**:413, 1924. (*e*) Halperin, G.: The Pathogenesis of Gastro-Duodenal Ulcer, Surg., Gynec. & Obst. **43**:173, 1926. (*f*) Morton, Charles B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer; a Consideration of Etiology, Ann. Surg. **85**:207 and 879, 1927. (*g*) Held, I. W., and Goldbloom, A. A.: Pathogenesis of Peptic Ulcer, M. Clin. North America **14**:319, 1930. (*h*) Alvarez, Walter C.: Light from the Laboratory and the Clinic on the Causes of Peptic Ulcer, Am. J. Surg. **18**:207, 1932.

2. Ivy, A. C.: Studies on Experimental Gastric and Duodenal Ulcer, Am. J. Physiol. **49**:143, 1919.

and diseased dogs at autopsy. Subsequently at autopsy on nine hundred dogs, only one chronic and one acute ulcer were found, each occurring in an animal that was diseased and cachectic.[3] In two hundred apparently normal cats and dogs, Mann [4] found no gastric lesion. Turck's [5] experience was also the same in examinations of one hundred and eighty-nine healthy and eighty-two diseased dogs. There is no satisfactory explanation of this apparent immunity to peptic ulceration possessed by the lower animals.

In addition to the difficulty of consistently producing ulcer experimentally, the early investigators were faced with the difficulty of producing chronic ulcer. It was relatively simple to produce acute ulcer, but it was not until 1923, when Mann and Williamson [6] published their method, that a technic was devised by which chronic ulcer could be produced with consistency. Previous to this there were reported only a few cases of characteristic punched-out or perforating ulcer.

In 1903 Watts,[7] with Sowers, performed anterior gastrojejunostomies on dogs. One dog died three months after the operation, and necropsy revealed a perforating jejunal ulcer opposite the stoma, with resulting peritonitis. Watts attributed this to the hyperacid gastric juice emptying directly into the jejunum. Montgomery [8] in 1923 studied the effect of hematoma and different types of suture material in anterior and posterior gastro-enterostomies in ten groups of experiments. He found only four ulcers in sixty dogs studied. Dott and Lim [9] had a somewhat similar experience. Borzkey,[10] Exalto [11] and von Roojen [12] observed jejunal ulcer after gastro-enterostomy, and the operation in man was

3. Ivy, A. C.: Contributions to the Physiology of the Stomach, Arch. Int. Med. **25**:6 (Jan.) 1920.

4. Mann, Frank C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, J. Exper. Med. **23**:203, 1916.

5. Turck, Fenton B.: Ulcer of the Stomach: Pathogenesis and Pathology, J. A. M. A. **46**:1753 (June 9) 1906.

6. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

7. Watts, S. H.: A Case of Peptic Ulcer in the Jejunum of a Dog Following Gastro-Enterostomy, with Review of the Cases Reported in Man, Bull. Johns Hopkins Hosp. **14**:191, 1903.

8. Montgomery, A. H.: Gastrojejunal Ulcer: An Experimental Study, Arch. Surg. **6**:136 (Jan.) 1923.

9. Dott, D. M., and Lim, R. K. S.: Experimental Jejunal Ulcer, Quart. J. Exper. Physiol. (supp.) **11**:109, 1923.

10. Borzkey, K.: Die chirurgische Behandlung des peptischen Magen- und Duodenalgeschwürs und seiner Komplikatione und die damit erreichten Endresultate, Beitr. z. klin. Chir. **57**:56, 1908.

11. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

12. von Roojen, quoted by Alvarez.[1h]

soon considered dangerous. Many other chance observations have been reported by the early investigators, but their detailed review would be superfluous here. More pertinent is the consideration of the production of ulcer in the study of the deviation of the alkaline duodenal juices. These will be discussed in combination and separately.

Probably the earliest recognition of the importance of the bile and pancreatic juices in preventing the formation of ulcer is that of Bickel,[13] who in 1909 made a rather interesting chance observation. In two dogs he performed duodenectomy after closure of the pylorus and gastroenterostomy to reestablish the continuity of the gastro-intestinal tract. The common bile and pancreatic ducts were sutured to the skin of the abdomen. One month later one dog died of perforation, with resulting peritonitis of one of several jejunal ulcers just distal to the stoma. Five years later Langenskiöld,[14] with the full realization of the importance of this work, published the results of his experiments, which eventually led to the more consistent procedure of Mann and Williamson.[6] He severed the duodenum just proximal to the opening of the bile duct and closed the distal ends. He then severed the jejunum several centimeters distal to the duodenum and anastomosed the distal end (end to end) to the proximal end of the duodenum and joined the proximal end of the jejunum to a loop of jejunum further caudad (end to side). In this manner the bile and pancreatic juices were shunted into the lower part of the small intestine. Because the animal appeared ill, it was killed, and an ulcer was found in the short segment of the duodenum between the stomach and the jejunum. This same procedure was repeated by McCann [15] in 1929, except that the proximal end of the severed jejunum was anastomosed to the terminal portion of the ileum (end to side), but ulcers developed in the jejunum rather than in the duodenum. By slightly modifying Langenskiöld's operation, Mann and Williamson [6] in 1923 proposed their "surgical duodenal drainage" procedure by which typical chronic ulcer could be produced consistently. Their operation consisted essentially in isolating the duodenum by severing it from the pylorus and the jejunum, closing its oral end and anastomosing its distal end to the terminal portion of the ileum from 25 to 75 cm. from the ileocecal junction and then anastomosing the proximal end of the jejunum to the pylorus. Fourteen of sixteen animals coming to necropsy showed typical subacute or chronic ulcer.

13. Bickel, A.: Beobachtungen an Hunden mit extirpiertem Duodenum, Berl. klin. Wchnschr. **46**:1201, 1909.

14. Langenskiöld, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, Skandinav. Arch. f. Physiol. **31**: 1, 1913.

15. McCann, James C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

Mann contended that there are two important factors in the causation and prevention of healing of such an ulcer, viz., a chemical and a mechanical factor. He stated that although the former has been recognized, the latter has not been sufficiently appreciated, and he emphasized the fact that the ulcer develops at the site where the mucosa was subjected to the greatest force of impingement of the gastric chyme as it was propulsed from the stomach in a nozzle-like manner. To emphasize this propulsive action further, Mann [16] performed the "surgical duodenal drainage" operation and then produced a typical hour-glass stomach in the prepyloric region, so that the stomach was divided into two pouches, communicating at the lesser curvature through a small opening. In this manner the propulsive power of the stomach was considerably lessened, and the animals were remarkably resistant to the development of ulcer. McCann [17] further stressed the importance of this mechanical factor by such suggestive evidence as the demonstration in one ulcer specimen of fifty or more hairs of the dog embedded in the sloping wall of the distal half of the crater. He surmised that the gastric chyme was thrown against this segment with sufficient force to embed the hairs in the wall of the ulcer.

The ulcers produced by the method of Mann and Williamson usually developed in from three to four weeks after operation and generally occurred on the posterior wall of the jejunum slightly to the right of the axial line and rarely involved the suture line. Usually there was only one ulcer, but occasionally there was a "kissing ulcer" and rarely a third ulcer. The occurrence of this third distal ulcer is explained by Mann rather fancifully as due to "a splash of the contents from the area of the first ulcer." These ulcers resembled in every way the ulcers found in man, being more or less circular and punched out, with overhanging edges; they always involved the entire thickness of the mucosa and usually penetrated the intestinal wall to a considerable depth.

The results obtained by the "surgical duodenal drainage" operation of Mann and Williamson have been corroborated by many others. Similar experiments were performed by Morton [18] on twenty dogs, and typical subacute chronic ulcer developed in all. Gallagher and Palmer [19] observed jejunal ulcer in thirty-eight of forty-seven animals on which

16. Mann, F. C.: The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, S. Clin. North America **5**:753, 1925.

17. McCann, J. C.: Further Studies in Experimental Peptic Ulcer: Chemistry of Experimental Ulcer, Proc. Staff Meet., Mayo Clin. **2**:284, 1927.

18. Morton, C. B.: Observations on Peptic Ulcer: V. Findings in Experimentally Produced Peptic Ulcer; Etiology and Therapeutic Consideration, Ann. Surg. **87**:401, 1928.

19. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30**:468, 1932.

the "duodenal drainage operation" was performed (an incidence of 70.2 per cent). They also noted that there was no relationship between the site of the duodenal secretion, whether high or low in the intestine, and the rapidity of the formation of the ulcer. A similar incidence was reported by Weiss and Gurriaran [20] in fifteen dogs. Neumann, de Moor and Deloyers [21] also noted a high incidence of ulcer after this operation. Jenkins and Palmer [22] attempted to minimize the importance of the mechanical factor so strongly emphasized by Mann and to strengthen the influence of the chemical factor. They performed the operation of Mann and Williamson, with the exception that the gastro-enterostomy stoma was modified by a side to side anastomosis, and ulcer developed in 90 per cent of the animals. They contended that they obtained just as high an incidence of ulcer when there was no mechanical injury due to the injection of chyme from a narrow stoma and strongly emphasized the importance of the chemical action of unneutralized gastric juice on the jejunal mucosa. This was verified by Matthews and Dragstedt,[23] who obtained ulcer in all of five dogs in which a large anastomosis was made between the stomach and the jejunum.

Morton [18] performed the operation of Mann and Williamson and produced typical chronic peptic ulcer in 50 per cent of the animals in which he had previously denuded mucosal areas on the lesser and the greater curvature. Delay in healing was much more marked on the lesser than on the greater curvature. Besides these lesions of the stomach, ulceration developed at the usual site in the jejunum in practically all animals. Even after a modified form of duodenal drainage in which the pyloric third of the stomach was resected so as to diminish the acid-secreting area of the stomach, ulcer usually developed in the jejunum. From an analysis of these and subsequent experiments, Morton [24] was inclined to favor the mechanical factor. He expressed the belief that the chronicity is probably due to a relative imbalance between the acids of the stomach and the alkaline juices of the duodenum,

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20. Weiss, A. G., and Gurriaran, G.: Ulcères chroniques expérimentaux crées par la dérivation des sucs alcalins duodénaux, Arch. d. mal. de l'app. digestif **20:** 63, 1930.

21. Neumann, F.; de Moor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères gastroduodénaux: Dérivation totale das sucs duodénaux, biliaires, et pancréatiques dans la l'iléon terminal, Compt. rend. Soc. de biol. **105:** 887, 1930.

22. Jenkins, H. P., and Palmer, W. L.: Studies on Experimental Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **28:**935, 1931.

23. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55:**265, 1932.

24. Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastroduodenal Analysis, Am. J. M. Sc. **177:**65, 1929.

causing incomplete or faulty neutralization of the acid gastric chyme. He [25] also stressed the possibility of an improper function of the pylorus.

Neumann, Deloyers and de Moor [26] obtained ulcers in 50 per cent of ten "surgical duodenal drainage" operations. Beaver and Mann [27] performed this same operation with the addition of preliminary sectioning of the vagus nerve in one group of animals and the splanchnic nerve in another. Ulceration developed in all except one in which vagotomy had been done. They concluded that sectioning of the gastric nerve did not prevent the formation of ulcer in that portion of the intestine receiving the gastric contents after removal of the alkaline secretions.

Owings and Smith [28] modified the procedure of Mann and Williamson by performing side to side anastomosis of the jejunum and stomach in twenty-six animals. Typical chronic ulcer developed in ten of the dogs. They then reconducted the duodenal secretion over the ulcerated areas in subsequent operations and obtained complete healing in four and partial healing in two of the animals. Similar healing was obtained by Morton,[18] who performed the "duodenal drainage operation," and at subsequent laparotomy, when an ulcer was found at the usual site in the jejunum, he performed gastro-enterostomy. From four to sixteen days after the latter procedure unmistakable signs of healing were found. Mann [29] also obtained healing by gastro-enterostomy after previously producing an ulcer by the "duodenal drainage" operation.

Thus it has been irrefutably established that deviation of all the alkaline duodenal juices will inevitably result in the formation of an ulcer. Mann attempted to explain this occurrence by the chemical and mechanical factors. It has been shown, however, that in spite of minimizing the latter, ulceration will develop in a high percentage of animals. However, the chemical factor cannot be abnegated so easily, as it is a much more tangible factor. The exact nature of the disturbed relationship between the acid gastric juice and the alkaline duodenal juices has not been satisfactorily explained.

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25. Morton, C. B.: Peptic Ulcer: IX. Chronic Lesions of the Duodenum Following Experimentally Produced Pyloric Dysfunction, Arch. Surg. **28**:467 (March) 1934.

26. Neumann, F.; Deloyers, L., and de Moor, P.: Contribution à l'étude de la pathogénie des ulcères duodénaux, Bull. Acad. roy. de méd. de Belgique **12**: 477, 1932.

27. Beaver, M. S., and Mann, F. C.: The Production of Peptic Ulcer After Section of the Gastric Nerve, Ann. Surg. **94**:1116, 1931.

28. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**:832, 1932.

29. Mann, F. C.: Production and Healing of Peptic Ulcer: An Experimental Study, Minnesota Med. **8**:638, 1925.

Boldyreff [30] maintained that the acidity of the gastric juice is regulated by the regurgitation of the duodenal alkali into the stomach. If this theory is accepted, these procedures would effect a persistent state of high gastric acidity, which might account for the production of ulcer. On the other hand, it is possible that the gastric acidity is independent of the regurgitation of the duodenal alkalis and that the ulcer is produced by the acid peptic acidity of the normal gastric chyme, which remains unbuffered or undiluted beyond the pylorus after deviation of the duodenal secretion. In order to determine which of these hypotheses is the more probable, experiments have been devised which produce a reflux of the duodenal secretions into the stomach.

Keppich [31] in 1921 performed experiments somewhat similar to those devised by Chlumsky [32] and Schmilinsky,[33] in which the proximal end of the upper part of the jejunum was anastomosed to the fundus of the stomach and the distal end to the pylorus (end to end) after the distal end of the duodenum was closed. In this manner the pancreatic, biliary and duodenal secretions must pass through the stomach to the jejunum. No ulcers formed after this procedure. On the other hand, McCann [15] repeated this procedure, except that he severed the duodenum at the pyloric sphincter, and obtained jejunal ulcer in 80 per cent of twenty-six dogs. The curious fact, shown by McCann, that there was no appreciable modification in the gastric acidity curve after this procedure may be elucidative. McCann's procedure was slightly modified by Weiss, Graves and Gurriaran,[34] so that instead of deviating duodenal secretion to the fundus it was deviated to the prepyloric region. Ulceration did not develop in any of fourteen dogs operated on. Graves,[35] working in the surgical experimental laboratory at Tulane University, performed similar experiments on eleven dogs with the same result and suggested that the acid gastric chyme was sufficiently mixed with the alkaline duodenal secretion to render it noninjurious to the jejunal mucosa. He also concurred with Weiss and his co-workers that trauma

30. Boldyreff, W.: The Self-Regulation of Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, Quart. J. Exper. Med. **8**:1, 1915.

31. Keppich, J.: Ueber das Ulcus pepticum jejuni nach Pylorusausschaltung, Zentralbl. f. Chir. **48**:118, 1921.

32. Chlumsky, V.: Ueber die Gastroenterostomie, Beitr. z. klin. Chir. **20**:231 and 487, 1898; Weitere Erfahrungen über die Gastroenterostomie, ibid. **27**:1 and 282, 1900.

33. Schmilinsky, H.: Die Einleitung der gesamten Duodenalsäfte in den Magen (innere Apotheke), Zentralbl. f. Chir. **45**:416, 1918.

34. Weiss, A. G.; Graves, A., and Gurriaran, G.: La dérivation intragastrique des sucs alcalins duodénaux, Compt. rend. Soc. de biol. **109**:916, 1932.

35. Graves, Amos M.: Combined and Separate Effects of Bile, Pancreatic Secretion, and Trauma in Experimental Peptic Ulcer, Arch. Surg. **30**:833 (May) 1935.

is of little or no importance. Ivy and Fauley [36] similarly rarely found ulceration after this operation. In contrast to these results, Fontaine and Kunlin [37] obtained ulcer complicated by profuse hemorrhage and perforation under similar circumstances and concluded that Boldyreff's reflex is of no consequence. Thus exists the maze of confusion and contradiction and the resulting difficulty obfuscating any effort to draw conclusions. About all that it is safe to assume is the undeniable fact that jejunal ulcer will usually develop if duodenal secretions are deviated. Which of these secretions, if any, plays a feature rôle? Is it the succus entericus, the pancreatic or the biliary juices? A variety of methods have been devised to determine this. Almost all have the underlying principle of exclusion of one or more of the juices. By excluding these juices either separately or in combination it has been possible to determine indirectly their protective influence against the formation of a peptic ulcer.

THE EFFECT OF THE COMBINED DEVIATION OF BILE AND PANCREATIC JUICES

Kehrer [38] in 1914 ligated the common duct and performed cholecystenterostomy and transplantation of the pancreatic duct into the terminal portion of the ileum. Of fifteen dogs operated on, multiple erosions and ulcers developed in the stomach in six, and one of these presented ulcers in the duodenum. Mann and Williamson [6] transplanted bile and pancreatic ducts into the terminal portion of the ileum in thirty-one dogs and noted ulcer in ten (33 per cent). This procedure left only the succus entericus to protect the duodenal mucosa. Graves [35] found peptic ulcer in the duodenum after performing duodenectomy in two stages, the first stage consisting of ligation of the common duct and cholecystenterostomy and transplantation of pancreatic duct into the jejunum and the second stage consisting of resection of the duodenum and gastrojejunostomy. Two of the four dogs operated on died after the first stage with perforating peptic ulcer and peritonitis. On the other hand, Owings and Smith [39] did not obtain ulceration after per-

36. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**:531, 1931.

37. Fontaine, R., and Kunlin, J.: Le reflex duodénal intervient- il dans la production des ulcères peptiques expérimentaux? Presse méd. **40**:1752, 1932; Ulcères peptiques expérimentaux obtenus par la dérivation des sucs intestinaux avec integrité du pylore, Compt. rend. Soc. de biol. **110**:294, 1932.

38. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwüres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:679, 1914.

39. Owings, J. C., and Smith, I. H.: The Etiology of Duodenal Ulcers, Proc. Soc. Exper. Biol. & Med. **29**:833, 1932.

forming similar operations. Of more than passing interest in this regard is the case reported by Morton and Graham,[40] in which a badly diseased gallbladder was excised, five stones were removed from the common duct and choledochostomy was performed. After removal of the tube and on the twelfth day after operation, complete obstruction occurred, acute symptoms of ulcer developed, and the patient died of an acute hemorrhage from a large duodenal ulcer, which was discovered at necropsy. They attributed the formation of the ulcer to interference with the discharge of alkaline pancreatic juice and bile into the duodenum by the biliary calculus. Bauer and Aron[41] resected the pancreas and left only a small amount for internal secretion, and two months later they ligated the common duct and anastomosed the gallbladder to the terminal portion of the ileum. No ulceration developed. Two and a half months later they resected the duodenum, and an ulcer developed in the jejunum distal to the gastrojejunostomy. They concluded that the duodenal secretion is most important in the protection against the formation of ulcer. Thus it is seen that the deviation of the combined bile and pancreatic secretions will result in a comparatively high incidence of ulcer; in other words, the duodenal secretion alone is not altogether sufficient protection against the formation of ulcer.

EFFECT OF THE ELIMINATION OF THE DUODENAL SECRETION ALONE

Mann and Williamson[6] performed duodenectomy and made the jejunum with the transplanted bile and pancreatic ducts occupy the place of the duodenum. Of ten dogs operated on, ulcer developed in two, three hundred and ninety-three days and five hundred and fifteen days after operation, respectively. Similar duodenectomy was performed by Mann and Kawamura[42] in the dog, cat, hog, goat and monkey, and careful observations were made for over two and a half years after operation. They concluded that the duodenum is of little, if any, importance in the life of these animals. Grey,[43] after similar experiments, came to the same conclusion. Weiss and Gurriaran[20] noted no difference in gastric acidity before and after operation. Graves[35] performed

40. Morton, C. B., and Graham, J. B.: Observations on Peptic Ulcer: VII. Clinical Corroboration of Experimental Data, Ann. Surg. **91**:73, 1930.

41. Bauer, R., and Aron, E.: Rôle respectif de la suppression des sécretions pancréatique et biliare, et de la résection duodénale dans la production des ulcères peptiques expérimentaux, Compt. rend. Soc. de biol. **113**:1063, 1933.

42. Mann, F. C., and Kawamura, K.: An Experimental Study of the Effects of Duodenectomy, J. A. M. A. **73**:878 (Sept. 20) 1919; Duodenectomy (An Experimental Study), Ann. Surg. **75**:208, 1922.

43. Grey, E. G.: Duodenectomy—Its Effect upon the Life of an Animal Transplantation of the Pancreatic Duct, Surg., Gynec. & Obst. **28**:36, 1919.

duodenectomy in three stages, and one animal lived eight and a half months after the last stage. This, in his opinion, offered indisputable evidence that the duodenum is not essential to life. Mann and Bollman,[44] on the other hand, concluded that duodenal mucosa and secretions are probably the most important factors in the prevention of the formation of peptic ulcer, with pancreatic juice next and bile of least importance.

THE EFFECT OF DEVIATION OF THE PANCREATIC JUICE

The importance of the combined bile and duodenal juices has been studied by eliminating the pancreatic juice either by total pancreatectomy, by ligation or transplantation of the pancreatic duct or by the production of a fistula in the pancreatic duct. With the exception of transplantation of the duct, all the procedures are open to serious objections, as the normal function is too greatly altered. Steinberg[45] performed total pancreatectomy in dogs with a Pavlov pouch and observed prolonged periods of active gastric secretion, a great increase in the concentrations of pepsin, longer periods of gastric retention and constant retching and vomiting. Whereas the chlorides of the gastric juice were uniform, the gastric juice was low in acid and high in pepsin during the continuous secretion. Postmortem examination revealed severe gastritis with a highly hemorrhagic mucosa. Similarly, Fauley and Ivy[46] had somewhat the same experience, although they also ligated the duct. Departing somewhat from the usual procedures, Grey[47] attempted to ascertain how the stomach would react to a more or less continuous influx of relatively strong alkaline fluid. This was provided for by transplanting the large pancreatic duct into the wall of the stomach of seven dogs after the lesser duct was ligated and divided. Grey observed only a moderate decrease in the acidity level of ingestion in later stages of digestion. Jona[48] made the general statement that ligation of the main pancreatic duct will result in ulceration of the duodenum and jejunum, but he did not give the number of dogs operated on or the incidence of ulcer. Berg[49] made observations on sixteen dogs deprived completely of pan-

44. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcer: Development and Treatment, J. A. M. A. **99**:1576 (Nov. 5) 1932.

45. Steinberg, M. E.: The Gastric Juice in Pancreatic Diabetes, Am. J. Physiol. **56**:371, 1921.

46. Fauley, G. B., and Ivy, A. C.: The Effect of Exclusion of Pancreatic Juice on Gastric Digestion, Am. J. Physiol. **89**:428, 1929.

47. Grey, E. G.: The Diversion of the Pancreatic Juice from the Duodenum into the Stomach: Its Effects upon the Level of Gastric Acidity and upon the Pancreas, J. Exper. Med. **26**:825, 1917.

48. Jona, J. L.: A Further Contribution to the Experimental Study of Duodenal Ulcer, M. J. Australia **1**:316, 1919.

49. Berg, Benjamin N.: Peptic Ulcers: Comparative Frequency After Deprivation of Bile and Pancreatic Juice, Arch. Surg. **28**:1057 (June) 1934.

creatic juice by means of fistulas made according to the technic of Rous and McMaster,[50] as adapted by Elman and McCaughan.[51] Daily rations of food were supplemented by sodium chloride administered intravenously in physiologic solution. All of the animals lost weight progressively and showed evidence of profound metabolic disturbances. Necropsy revealed definite and marked degenerative changes in the liver, and peptic ulcer was found in only one animal, which was one of the three in which jaundice developed. This, according to Berg, indicated that the absence or neutralization of gastric acidity by pancreatic juice is not an important factor. Another publication by Berg and Zucker,[52] dealing with similar experiments, reported the same results. Berg and Jobling [53] noted no lesions in a series of nine dogs with pancreatic fistulas. Graves [35] found no ulceration in a series of twelve dogs in which the pancreatic duct was transplanted into the distal end of the jejunum. Of this group, six were subjected to a second stage operation in which the duodenal secretions and bile were drained into the ileum, and the jejunum with its pancreatic duct was anastomosed to the stomach. Five dogs died of ulcer, complicated with perforation in three and with hemorrhage in two. Loewy [54] anastomosed the pancreatic duct to the right ureter in four dogs and produced a pancreatic fistula in one dog. He observed no ulceration in any of the five dogs and concluded that the absence of pancreatic juice in the duodenum is not responsible for the formation of ulcer. A similar observation was made by Owings and Smith,[39] who transplanted the pancreatic duct into the jejunum 18 inches (45 cm.) below the ligament of Treitz in one group of animals. Neumann, Deloyers and de Moor [55] also observed no ulceration in six dogs in which the main pancreatic duct was ligated and the accessory pancreatic duct transplanted into the terminal portion of the ileum. In a subsequent publication [26] they reported the absence of ulceration in a series of eight dogs operated on in the same manner.

50. Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts as Applied to the Common Duct, J. Exper. Med. **37**:11, 1923.

51. Elman, Robert, and McCaughan, John M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, J. Exper. Med. **45**:561, 1927.

52. Berg, B. N., and Zucker, T. F.: Liver Changes After Deprivation of External Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **29**:68, 1931; Comparative Frequency of Peptic Ulcers After Deprivation of Bile and Pancreatic Juice, ibid. **30**:330, 1932.

53. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcer, Arch. Surg. **20**:997 (June) 1930.

54. Loewy, G.: Influence de la dérivation du suc pancréatique sur la production des ulcères duodénaux, Compt. rend. Soc. de biol. **111**:783, 1932.

55. Neumann, F.; Deloyers, L., and de Moor, P.: Les ulcères duodénaux, Arch. d. mal. de l'app. digestif **21**:511, 1931.

Zucker, Newburger and Berg,[56] in studying the inorganic constituents of blood and urine in dogs with pancreatic fistula, made no mention of the formation of ulcer in observations on twenty animals. In contrast to the foregoing findings, Elman and Hartmann [57] found duodenal ulcer in each of six dogs in which there was a continued loss of pancreatic juice. These dogs were kept alive for about thirteen days with the intraperitoneal administration of Ringer's solution. As a result of a 100 per cent incidence of ulcer, they felt justified in assuming that the presence of pancreatic juice in some way protects the duodenum against the formation of ulcer and that bile plays a minor rôle as compared to pancreatic juice. Matthews and Dragstedt [28] also observed chronic duodenal ulcer in dogs with a fistula in the pancreatic duct and stated that their formation could be prevented by the oral administration of calcium carbonate or finely ground meal. Hoerner [58] reported a curious but interesting observation. After evulsion of the pancreatic duct no lesion was found in the gastric or duodenal mucosa, but when a fistula of the pancreatic duct was established, peptic ulcer developed in 42 per cent of the animals. In the dogs in which ulcer developed, a check of previous determinations revealed an increase in the amount of gastric secretion and acidity, which was in definite contrast to the results obtained in the other animals of the series in which no lesion developed.

THE EFFECT OF THE BILIARY SECRETION ALONE

The influence and the effect of the biliary secretions have been studied by methods similar to those used in the study of the pancreatic juice. Kapsinow [59] in 1926 was one of the first investigators to observe the effect of bile excluded from the duodenum by cholecystnephrostomy. In this manner he overcame the objection of possible ascending infection of the biliary tract, intestinal trauma and the possibility of any bile finding its way into the intestine. He performed the operation in two stages: (1) cholecystnephrostomy and, at a later date, when healing was complete, (2) ligation and division of the common bile duct. Of forty-three animals operated on, typical duodenal ulcer developed in seventeen (39.5 per cent). In two instances there was definite perfora-

56. Zucker, T. F.; Newburger, M. S., and Berg, B. N.: Inorganic Constituents of Blood and Urine in Dogs with Pancreatic Fistula, Proc. Soc. Exper. Biol. & Med. **27**:666, 1930.

57. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

58. Hoerner, M. T.: The Effect of Exclusion of the Pancreatic Juice from the Duodenum: An Experimental Study, Proc. Staff Meet., Mayo Clin. **9**:473, 1934.

59. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestines, Ann. Surg. **83**:614, 1926.

tion. Neumann, Deloyers and de Moor [55] performed cholecystenterostomy near the terminal portion of the ileum after ligating the common duct and obtained chronic duodenal ulcer in five of seven dogs operated on (70 per cent). The dogs remained in excellent health until ulceration developed, and the gastric acidity did not change appreciably before or after operation. The authors performed this same operation again on two other series, one of seven [60] and another of eight dogs,[26] and obtained ulceration in 57 and 62.5 per cent, respectively. Weiss and Gurriaran [20] performed the same operation on a series of three dogs, in one of which an ulcer developed. A similar operation was performed by Owings and Smith,[39] except that the cholecystenterostomy was performed at a higher level, about 18 inches below the ligament of Treitz. Acute duodenal ulcer developed in two of five dogs. Similarly Graves,[35] in a series of eight dogs, obtained one completely healed duodenal ulcer, which produced stenosis.

The protective influence of bile was rather convincingly demonstrated by Ochsner, Gage and Hosoi [61] while working in the experimental surgical laboratory at Tulane University. They performed a gastric pouch of the Heidenhain type from the greater curvature and of the Pavlov type from the lesser curvature plus anastomosis of the proximal portion of the jejunum to the pouch. They obtained ulcer in 100 per cent of the animals on which the former procedure was done and in 71 per cent in which the latter was done, or an average of 85 per cent. In another series in which the procedure was similar to the foregoing, but with the addition of anastomosis of the fundus of the gallbladder to the pouch, the incidence of ulcer was reduced from 100 to 28 per cent in the dogs with a pouch in the greater curvature and from 71 to 50 per cent in the animals with a pouch in the lesser curvature, or from an average of 85 per cent in the former series to 39 per cent in the latter group.

Exclusion of bile by the fistula method has also been a popular procedure for determining its effect. Rous and McMaster [50] described an excellent method for the permanent sterile drainage of a common bile duct. They used this method on seventeen dogs over a period ranging up to three months and observed that the animals remained in good health throughout except for some anemia. They made no mention of ulcer occurring. Berg, Johnston and Jobling,[62] using this same method for the production of an external biliary fistula in a series of nine dogs

60. Neumann, F.; de Moor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères gastro-duodénaux. Dérivation exclusive de la bile dans l'iléon terminal, Compt. rend. Soc. de biol. **105**:890, 1930.

61. Ochsner, A.; Gage, M., and Hosoi, K.: The Relationship of Peptic Ulceration to Gastric Chemism, Proc. Soc. Exper. Biol. & Med. **31**:1260, 1934.

62. Berg, B. N.; Johnston, A., and Jobling, J. W.: Duodenal and Gastric Ulcers in Dogs with Biliary Fistulas, Proc. Soc. Exper. Biol. & Med. **25**:334, 1928.

living from twelve to forty-six days, observed duodenal ulcers in seven animals, an incidence of 77.7 per cent. They also noted that all the dogs lost an average of 25 per cent in weight. Two years later Berg and Jobling [53] reported the results in another series of twenty-three dogs on which a similar procedure had been performed, but in which there was an uninterrupted flow of bile, an intermittent flow of bile or complete biliary obstruction. In thirteen of the twenty-three dogs a duodenal or gastric lesion developed, an incidence of 56.5 per cent. Because of the observation that under poor environmental conditions and poor preparation of food, ulceration developed in 100 per cent of their animals, whereas under improved conditions the incidence diminished to 13 per cent, the authors suggested that the formation of ulcer was in some way related to the environment. They also opined that probably one of the effects of the exclusion of bile may be the disturbance of the regulatory mechanism of the secretion of mucus, which exposes the surface of the epithelium to the action of the gastric juice.

Another method of studying the influence of bile in the formation of peptic ulcer is by excluding the duodenal and pancreatic secretions. Graves [35] accomplished this by transplanting the common bile duct into the jejunum as the first stage and at a subsequent date (average thirty days) performing "surgical duodenal drainage" and substituting the jejunum with its common duct transplant. Of six dogs operated on, one died of pneumonia on the tenth postoperative day, and although no ulcer was found, erosion was present about the silk sutures. The five remaining dogs died in from twenty-two to fifty days with ulceration of the jejunum complicated by perforation or hemorrhage. Neumann, de Moor and Deloyers [63] achieved the same end by performing end to end anastomosis of the stomach and the jejunum, and instead of transplanting the common duct they ligated and anastomosed the gallbladder to the jejunum just distal to the gastrojejunal anastomosis. They did a one stage operation and noticed that the procedure was long and shocking. Of six dogs operated on, two presented definite ulceration, and jejunitis developed in two.

If an attempt is made to summarize or draw conclusions from this bewildering and confusing maze of contradictory experimental results, it is found that: 1. There is progressively diminishing immunity to the formation of ulcer from the duodenum aborally. 2. Probably the reflux of the entire duodenal contents of the stomach, particularly in the prepyloric region, will prevent the formation of ulcer or actuate healing if ulcer has already formed. 3. Deviation of the duodenal, biliary and pancreatic alkaline secretions will more consistently produce ulcer than

63. Neumann, F.; de Moor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères duodenaux. Dérivation des sucs duodénaux et pancréatiques dans l'iléon terminal, Compt. rend. Soc. de biol. **105**:892, 1930.

the isolated deviation of each. 4. Probably bile is more influential than pancreatic juice or duodenal secretion alone in the protection against the formation of ulcer. 5. Possibly the pancreatic juice is more effective than duodenal secretions alone in the prevention of the development of ulcer.

Because of the present day shadows cast on the experimental results by the overhead clouds of doubt, contradiction and insolvability, this investigation was attempted. One of the chief difficulties in attempting to draw conclusions is the somewhat risible, but almost exasperating, ability of two investigators performing the same procedure to obtain diametrically opposite results—witness Berg's and Elman and Hartmann's findings in deviation of pancreatic juice. Much of this diversity is due to comparisons made by different observers and under different circumstances. Thus, it would appear that if there is an equalization of extraneous factors, a much better basis for comparison could be made with the resulting stronger grounds for the drawing of conclusions. In the following experiments an attempt is made to evaluate the relative protective value of the constituents of the alkaline duodenal juices, viz., the succus entericus, the bile and the pancreatic juice. Each group of experiments is characterized by a similar procedure, so that they all have a common denominator. However, each group has one added change which may account for any difference in results obtained, as all the other factors are equal. Under such rigidly controlled experiments there can be little objection to comparisons, and more convincing conclusions can be drawn.

AUTHOR'S EXPERIMENTS

Material and Method.—Before any dog was used for the operative procedure it was first observed for a short time to determine with some degree of certainty that it was acclimated to the environment of the kennel. Only healthy, moderately large dogs, free from any evidence of distemper, infection or pregnancy, were used. In all of the surgical procedures the following postoperative routine was instituted. An intravenous infusion of warmed 5 per cent solution of dextrose containing normal lactate-Ringer solution was given into the external jugular vein immediately after the operation. The amount used was based on the dosage of 50 cc. per kilogram of body weight. Similar infusions were given once daily for the following three days. The next three days the dog was allowed to have water and was fed equal parts of milk and Karo corn syrup morning and afternoon. On the seventh postoperative day, it was returned to a normal stock kennel chow diet. Usually on the first or second postoperative day the dog appeared active, stood on its feet, wagged its tail and took a normal interest in the surroundings.

All the ulcers were studied microscopically in order to corroborate definitely the gross changes. Necropsy was performed immediately after the death of the dog, and the specimen was fixed at once in a large quantity of 10 per cent dilution of solution of formaldehyde U. S. P. or Zenker's fixative. General histopathologic study was performed by the utilization of the hematoxylin and eosin stain, and the study of evidence of increased fibrosis was facilitated by the use of Mallory's aniline blue stain.

In the consideration of the experimental findings of peptic ulceration it is always best to begin with a common understanding of the definition of terms. A distinction must be made between a mucosal erosion and a true peptic ulcer. Between the mucosa and the submucosa of the dog there is a prominent band of muscle referred to as the muscularis mucosae. Any localized mucosal defect extending only to or occasionally partially involving this muscularis mucosae is considered as an

Fig. 1.—Drawing of the completed operative procedure performed on the dogs in group 1. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy.

erosion, whereas a true peptic ulcer is a mucosal defect which has penetrated the muscularis mucosae with its base well in the submucosa or resting on or partially involving the muscularis propria. Penetration through this muscularis propria and opening into the general peritoneal cavity or having a base formed by another viscus, such as the liver, spleen, pancreas or diaphragm, is referred to as a perforated ulcer (fig. 2).

Grossly the ulcers had the characteristics of the subacute and chronic ulcers in man. The ulcerated area was usually round, but occasionally oval, with the long axis parallel to the long axis of the intestines. Of particular interest is the site of the ulcer. In order to have a thorough and common understanding, a definition of terms is again apropos. A gastric ulcer is one found anywhere in the stomach proper. A jejunal ulcer is one located in the jejunum, usually near the gastrojejunal anastomosis (fig. 2). A gastrojejunal anastomotic ulcer is one situated at the suture line of anastomosis (fig. 3).

Microscopically, these ulcers resembled the typical subacute and chronic ulcers seen in man, although some of them had acute and sub-

Fig. 2 (group 1, dog 54).—Pyloric occlusion and gastrojejunostomy were performed. Note the perforated ulcer in the efferent loop of the jejunum.

acute characteristics. The subacute ulcers were typified by rapid and deep penetration into the muscle layers with a steep wall (fig. 4). Frequently the process progressed so rapidly that adhesions had no time to form, and complete perforation resulted. In some the diameter at the mucosal level was greater than at the base, so that the edge of the ulcer had a sloping or terraced appearance. There was only a moderate fibroblastic reaction, with some lymphoid and round cell infiltration. Thrombosed vessels and hemorrhage were occasionally noted in the deeper layers. There was only a moderate amount of granulation tissue. In some there was a marked, acute inflammatory reaction about the crater with definite induration and leukocytic infiltration.

In the majority of chronic ulcers the crater was deep, involving all the muscular layers with a dense fibrotic base. This was excellently

demonstrated by the Mallory stain. The edges were definitely raised and somewhat overhanging. The thickness of the fibrotic base varied from a rather thin layer to a thick, dense, contracted base with some distortion. Frequently the wall of the ulcer on the proximal side was steep and markedly elevated, whereas the distal side appeared gently sloping. This characteristic is explained by Aschoff [64] as due to the passage of food across it, producing a slipping of the mucosa partly over the ulcer. On the inner surface there was usually present a layer of fibrin, necrotic tissue and cellular exudate, varying in thickness and depending on the existing degree of healing. The mucosa appeared

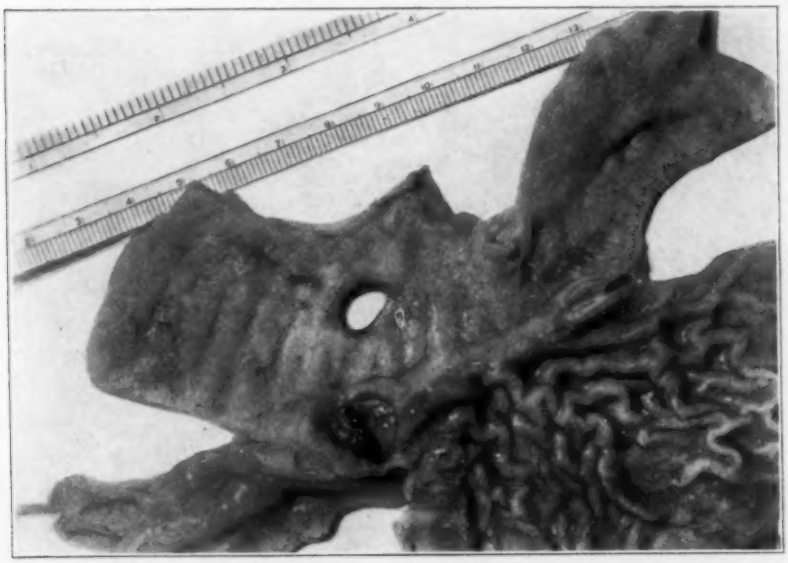

Fig. 3 (group 3, dog 68).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. A perforated ulcer is shown in the efferent loop of the jejunum. Note also the anastomotic ulcer opposite the perforated ulcer. The anastomotic ulcer is of the chronic, fibrotic type. Two black silk sutures can be seen at the base of the ulcer hanging free into the lumen.

thickened, was definitely proliferated and produced a picture of an overhanging edge or recess formation beneath it, as a result of the sloughing away of the submucosa (fig. 4). The greatest thickening of the base was at the periphery, and the adjacent muscular wall appeared receded. Also in the periphery there was considerable lymphocytic and plasma cell infiltration in all the layers. A few mononuclear and polymorpho-

64. Aschoff, L.: Lectures on Pathology (delivered in the United States, 1924), New York, Paul B. Hoeber, Inc., 1924.

nuclear cells were seen in the mucosa and submucosa. Varying degrees of infiltrating granulation were always present beneath the exudative layer and at the periphery beneath the submucosa.

GROUP 1.—*Pyloric Occlusion and Gastrojejunostomy.*

Method.—With the dogs under ether anesthesia and rigid aseptic precautions, a right paramedian incision was made. Hemostasis in the wound was secured by ligation of bleeding vessels with no. 00 plain catgut. The pylorus and duodenum were delivered into the wound. The right gastric and right gastro-epiploic arteries were divided between clamps and ligated with no. 1 plain catgut. The site was then well packed off with wash cloths soaked in hot saline solution to catch any spillage. Crushing clamps were not used in any of the procedures. The pyloro-duodenal junction was divided, and both ends were closed by successively incising them for a small distance and closing the incisions with a hemostatic whip-over

Fig. 4.—Low power photomicrograph of a subacute jejunal ulcer. Note the recess formation beneath the epithelium on either side, resulting in the appearance of undermined edges. Perforation was prevented in this ulcer by the omentum, which sealed over the base of the ulcer on the serosal side. The base of the ulcer is shown as this omental covering.

suture of no. 00 chromic catgut. These ends were inverted by a continuous Lembert stitch of black silk. In order to reestablish continuity of the gastro-intestinal tract, an anterior gastrojejunostomy was performed. The jejunum just distal to the ligament of Treitz was delivered into the wound as well as the lower end of the corpus of the stomach. An isoperistaltic anastomosis was performed, the antimesenteric border of the jejunum being used. Two stay sutures of black silk were first introduced, approximately 3.5 cm. apart. The stoma was about 2.5 cm. in length. The hemostatic and serosal sutures consisted of no. 00 chromic catgut and black silk, respectively. The abdominal wound was closed by using a continuous black silk suture for the peritoneum and a similar suture for the sheath of the rectus muscle. The edges of the skin were approximated with a continuous interlocking stitch of black silk. This surgical procedure was usually performed in from forty-five to fifty minutes.

Results.—This group consisted of twenty dogs, which lived from nine to two hundred and seventy-one days after operation. Immediate recuperation from the operation in the majority of the animals was astonishingly rapid. However, after about the third postoperative week anorexia began to develop in some of the dogs, particularly those with ulceration, and they lost weight rapidly. Whereas those dogs in which ulcer was noted at autopsy lived an average period of forty-two days after operation, the dogs without ulcer had an average postoperative duration of seventy-four and four-tenths days. The average postoperative duration in days for the twenty animals was fifty-eight and two-tenths, or about two months.

In ten of the twenty dogs ulcer was not found at necropsy. Four dogs without ulceration died of pneumonia twenty, twenty-five, thirty-nine and sixty-nine days after operation, respectively, after sufficient time for the ulcer to develop had elapsed. Two of the animals died twenty-six and sixty-two days, respectively, after operation of an apparently unaccountable inanition. These dogs never maintained

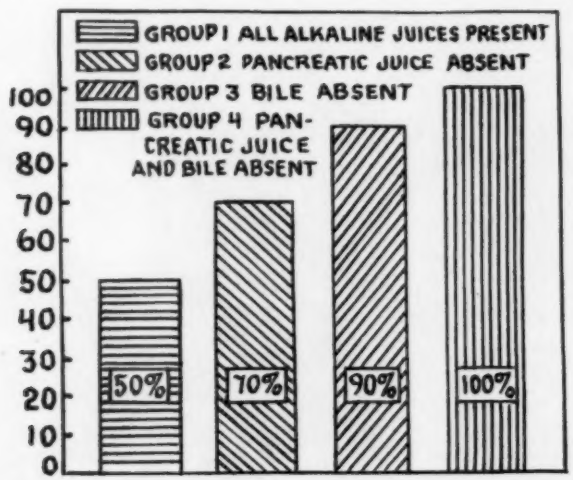

Fig. 5.—Graph showing the incidence of ulcer formation in the respective groups of dogs.

a normal appetite and about one week before death lost weight rapidly. Two other animals, which died forty-two days after operation, had a somewhat similar clinical manifestation but at necropsy presented evidence of a massive gastrointestinal hemorrhage. The stomach, jejunum and ileum and even the upper portion of the colon were filled with old blood, some of which appeared altered. The exact cause of this could not be definitely determined. However, it was believed to be due to gastritis and jejunitis as the mucosa in this region showed some congestion and small petechial areas. One dog, dying one hundred and fifty-five days after operation, had in the right ventricle a large number of dirofilaria, which was in all probability the cause of death, as no other abnormalities were found. The last animal of this group was still in good health two hundred and seventy-one days after operation, at which time it was finally killed, but no lesion was found.

In the remaining ten dogs, or 50 per cent, ulcer developed (fig. 5). All of the ulcers were of the typical subacute and chronic type. The shortest postoperative duration in this group was nine days, the longest one hundred and four days and

the average forty-two days, or six weeks. Of the ten dogs with ulceration, there were seven, or 70 per cent, which died of perforation and general peritonitis (fig. 2). Another dog presented a perforated ulcer, which was plastered against the liver and had eroded into it. One dog, dying fifty-three days after operation, showed no evidence of perforation or other complication. The tenth dog died one hundred and four days after operation of intussusception of the ileum with an associated mesenteric thrombosis. Besides this, there were two jejunal ulcers present.

There were only two dogs, or 20 per cent, of the ten in which more than one ulcer developed, and in each of these there were two ulcers. These ulcers varied in size from 0.5 to 2 cm., but in the majority they were approximately 1 cm. in diameter.

In the group of ten dogs all the ulcers were jejunal and located at approximately the same site, i. e., in the efferent loop of the jejunum opposite the anastomosis on the antimesenteric border slightly anteriorly (fig. 2). The consistency of this characteristic location demands some explanation. There is certainly no reason to attribute this to trauma, because this would be expected to occur in the jejunum immediately opposite the anastomosis rather than in the efferent loop. A more plausible and attractive explanation is the chemical theory. The alkaline duodenal contents in draining down the intestine must pass from the afferent side of the anastomosis toward the efferent loop. No neutralization with gastric chyme occurs until the alkaline juices encounter the acid chyme opposite the anastomosis. Thus, the afferent loop and that portion of the jejunal mucosa opposite the anastomosis are protected by the normal alkaline juices. However, the greater degree of this neutralization has occurred when the alkaline juices have reached the efferent loop, and little alkalinity remains to protect this portion of the jejunal mucosa, thus there being greater likelihood of the development of ulceration.

GROUP 2.—*Pyloric Occlusion, Gastrojejunostomy and Deviation of Pancreatic Juice.*

Method.—In this group of dogs the effect of the deviation of pancreatic juice was determined. The same procedure as that used on group 1 was performed, but in addition the main pancreatic duct was transplanted into the terminal portion of the ileum in the following manner (fig. 6). The small accessory pancreatic duct, which enters the duodenum about 0.5 cm. below the papilla of Vater, was identified and divided between ligatures. The larger, main pancreatic duct, which enters the duodenum about 4 cm. below the papilla of Vater, was identified and reamed out of the duodenum so that there remained attached to its os approximately 2 cm. of duodenal mucosa, submucosa, muscularis and serosa. The resulting defect in the duodenum was immediately closed with a single row of Lembert's sutures. A loop of ileum was then brought up and a site chosen about 30 mm. from the ileocecal junction. Two black silk sutures were introduced through its medial wall into the lumen and out through a small stab wound in the opposite side of the bowel. These sutures were then passed through the small margin of the wall of the duodenum surrounding the os of the pancreatic duct and brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near their origin. By carefully pulling these sutures taut, the pancreatic duct was drawn through the stab wound and into the lumen of the ileum. It was secured in place by tying these sutures. In order to avoid any undue tension on the sutures holding the pancreatic duct in the lumen, the ileum was approximated to the duodenum by a few Lembert sutures. This surgical procedure was usually performed in approximately fifty-five minutes.

Results.—This group consisted of ten dogs, which lived from seven to fifty-six days after operation. Rapid immediate recovery from the operation with maintenance of normal appetite and weight characterized all the animals. It was not until about one week before they succumbed that they began to show loss of appetite, rapid decline in weight and progressive weakness and apathy.

The shortest postoperative duration was seven days, the longest fifty-six days and the average thirty-four and six-tenths days. Three dogs, dying fifteen, seventeen and thirty-eight days postoperatively, showed no evidence of ulceration in the stomach, duodenum or jejunum. In each instance the cause of death could not be definitely determined at necropsy and was attributed to inanition. The transplanted

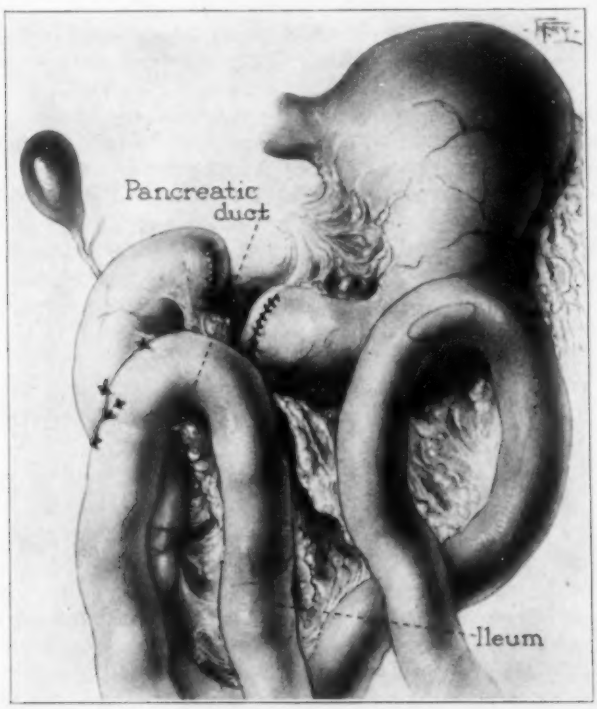

Fig. 6.—Drawing of the completed operative procedure performed on the dogs in group 2. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The accessory pancreatic duct was ligated and severed, and the main pancreatic duct was transplanted into the terminal portion of the ileum.

pancreatic duct was found to be patent and apparently functioning satisfactorily. The pancreas was grossly normal; microscopic study revealed no abnormal changes. Careful dissection of the pancreas from the duodenum was performed in every instance at necropsy to exclude the possibility of some pancreatic secretion still draining into the duodenum.

Of the ten dogs in this group, there were seven in which ulcer developed, an incidence of 70 per cent (fig. 5). Five of the seven had perforated ulcers, with resulting peritonitis. In two there was no perforation, but a large amount of blood was found in the gastro-intestinal tract, much of which appeared altered.

The ulcers ranged in size from 1 to 2 cm. in diameter and were usually round or oval. In four instances (57 per cent) there was more than one ulcer present (fig. 7). Of particular interest in this group is the variation in position of the ulcer. In two animals anastomotic ulceration in the efferent portion of the suture line was present. The first dog, dying fifty-one days after operation, had two ulcers, one in the efferent loop of the jejunum of the subacute variety and the other in the suture line. The anastomotic ulcer was of the chronic variety, with thick, indurated, overhanging edges and a hard, fibroblastic base, with two loose black silk sutures hanging free from the center. In six of the seven dogs there was an ulcer in the efferent loop of the jejunum in approximately the same location as in group 1. In one instance there were two ulcers in the efferent loop of the jejunum

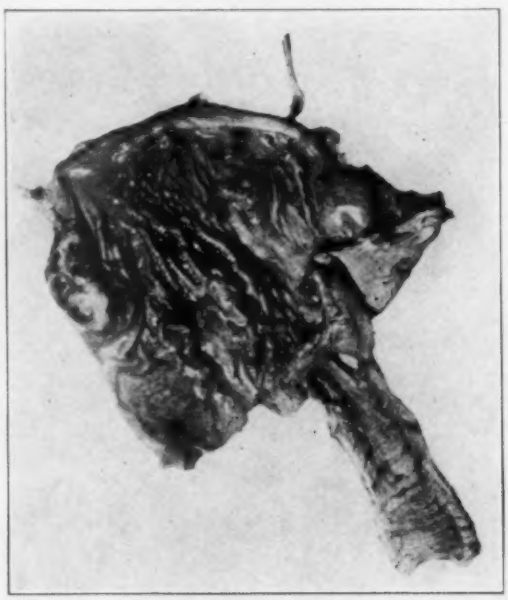

Fig. 7 (group 2, dog 96).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the pancreatic duct into the terminal portion of the ileum were performed. Two subacute and chronic ulcers are shown in the efferent loop of the jejunum. One ulcer has perforated. Note that these ulcers lie immediately opposite each other and appear as mirror images of each other, except that one has perforated. This is referred to as a "contact" or "kissing" ulcer.

exactly opposite each other, or the "kissing" type, one of which perforated (fig. 7). In only one dog, dying forty-six days after the operation, there was an ulcer immediately opposite the stoma, and in this instance there were two other ulcers of the subacute variety lying just caudad or in the jejunum on the efferent side of the stoma. Of more than passing interest, because it was not observed in the previous group, was the occurrence of ulcers in the jejunum on the efferent side of the stoma. Both of these were of the acute and subacute types. However, in one of these dogs, dying fifty-six days after operation, another large ulcer of the chronic variety was found in the efferent loop of the jejunum, as in group 1.

GROUP 3.—*Pyloric Occlusion, Gastrojejunostomy and Deviation of Bile.*

Method.—The same procedure as that used on Group 1 was performed, but in addition the common bile duct was transplanted into the terminal portion of the ileum in the following manner (fig. 8): The common bile duct was identified and dissected free for approximately 2 cm. at its distal end. Two mosquito forceps were applied to the duct just proximal to its entrance in the duodenum, and it was sectioned between these. The distal end was doubly ligated with black silk. The proximal end was then split upward for about 2 mm., and mosquito forceps were applied to each "lip." A loop of the terminal portion of the ileum was brought up, and a site about 20 cm. from the ileocecal junction was chosen. Two black silk sutures were introduced through its medial wall into the lumen and

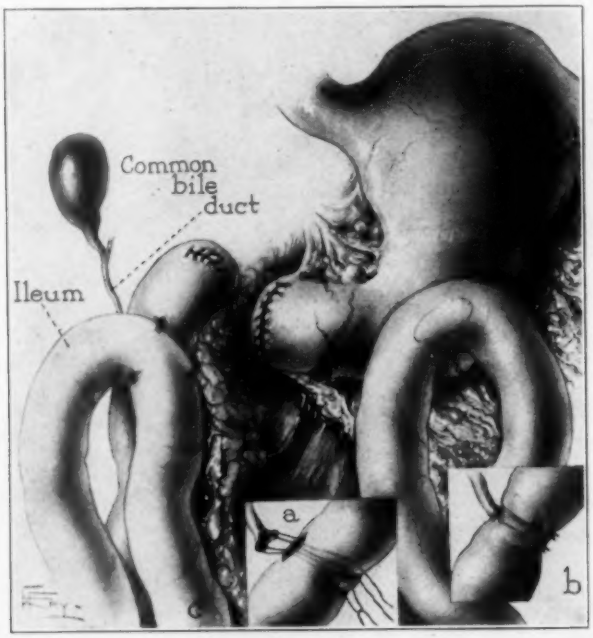

Fig. 8.—Drawing of the completed operative procedure performed on the dogs in group 3. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by gastrojejunostomy. Note the drawings in the lower right corner, illustrating the technic of transplantation of the common bile duct into the terminal portion of the ileum. (The pancreatic duct was transplanted by a similar technic.) In *a*, two black silk sutures have been introduced through the medial wall of the ileum into the lumen and out through one of the "lips" of the split common bile duct and then brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near the origin of the suture. In *b*, the common bile duct has been drawn through a stab wound into the lumen of the ileum and secured by tying the sutures.

out through a small stab wound placed in the opposite side. Each suture was passed through one of the "lips" of the split common bile duct and then brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near the origin of the suture (fig. 8*a*). By carefully pulling these

sutures taut, the common bile duct was drawn through the stab wound into the lumen of the ileum and then secured by tying the sutures (fig. 8*b*). In order to avoid any undue tension on the sutures holding the common duct in the lumen, the ileum was approximated to the duodenum by a few Lembert sutures. At autopsy the ducts were carefully dissected and found to have healed satisfactorily (fig. 9). This surgical procedure usually required about fifty-five minutes.

Results.—This group consisted of twenty dogs, which lived from seven to sixty days after operation. The majority of the animals recovered from the operation rapidly and maintained normal appetite and weight for a short period of time, and then anorexia, progressive loss of weight, evidences of inanition and weakness began to develop, and the animals eventually died. In contrast to the animals in

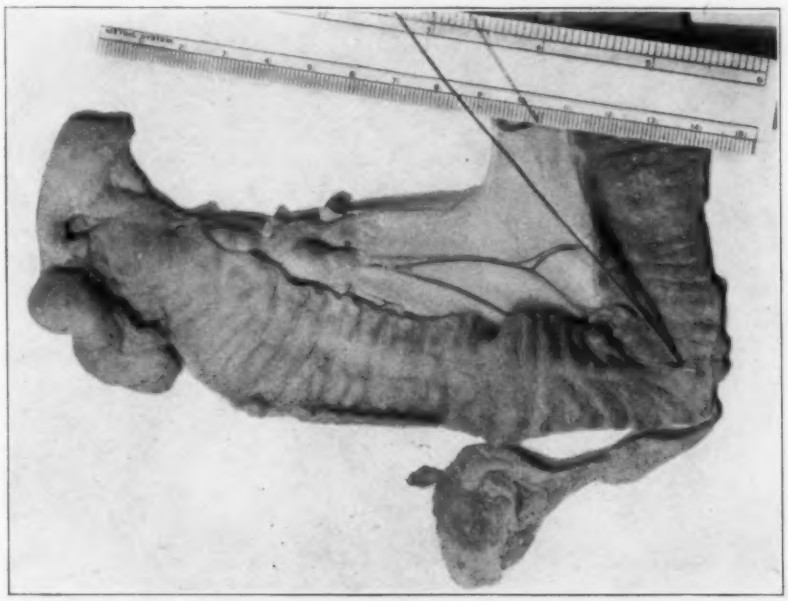

Fig. 9 (group 3, dog 74).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of ileum were performed. The photograph shows the terminal portion of the ileum and the transplanted common bile duct. Straw has been passed through opening of transplanted duct in the wall of the ileum. Note the cecum and the appendix at the extreme right of the picture.

group 1, for which the average postoperative duration of life was fifty-eight and two-tenths days, or about two months, the postoperative duration for this group was twenty-nine and eight-tenths, or about one month. This difference is sufficiently pronounced to be of some significance and will be discussed later.

Two of the dogs, dying nineteen and forty-two days, respectively, after operation, presented no evidence of peptic ulceration. However, in the latter, an unusually large number of intestinal worms were found in the jejunum and ileum. The jejunum, ileum and cecum and the upper portion of the colon were literally packed with blood, some of which appeared to be altered. When the mucosa was washed clean, the heads of the worms were found embedded in the mucosa, which

appeared congested with many small petechial areas. In all probability, this was the cause of the massive oozing of blood. The other dog also presented clinically inanition and toxemia, and at necropsy massive gastro-intestinal hemorrhage was also found. The mucosa of the stomach, duodenum and jejunum appeared congested with petechial areas scattered throughout. Gastritis and jejunitis were undoubtedly present, but no obvious erosion or ulcerations.

Of the twenty dogs in this group, ulcer developed in eighteen, or 90 per cent (fig. 5). All of the ulcers were of the typical subacute and chronic type. The

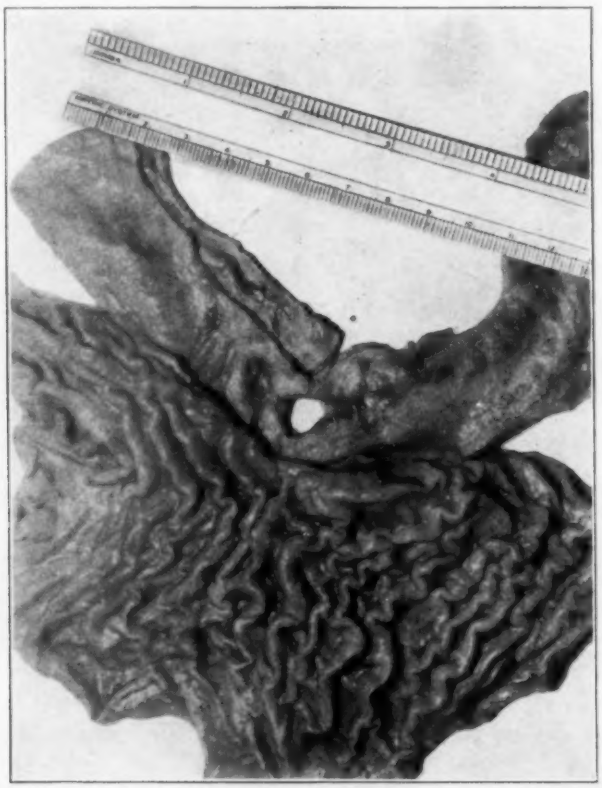

Fig. 10 (group 3, dog 79).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. Two ulcers of the jejunum are shown, one of which has perforated. Note that one ulcer is immediately opposite the stoma, and the other is in the efferent loop. There is only a small margin of jejunal mucosa between the two ulcers.

shortest postoperative duration was seven days, the longest sixty days and the average about thirty days. Perforation occurred in thirteen of the eighteen dogs, an incidence of 72.2 per cent. Perforation into the general peritoneal cavity with resulting peritonitis occurred in ten of the thirteen dogs (fig. 10). Necropsy on two of the animals, dying twenty-two and twelve days postoperatively, respectively, revealed interesting changes. In both animals the anterior wall of the jejunum

at the site of the gastrojejunostomy was found adherent to the left leaf of the diaphragm, and the jejunal ulcer had ruptured through the diaphragm into the left pleural cavity, with resulting pleurisy and pneumonia. The remaining animals with a perforating ulcer also revealed an interesting observation. The jejunal ulcer was intimately adherent to one lobe of the liver and had perforated into this viscus with erosion of its parenchyma. In one dog, which died of pneumonia seven days after operation, a large subacute jejunal ulcer had already developed, thus revealing how early an ulcer may occur. One dog, dying only thirteen days after

Fig. 11 (group 3, dog 71).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. A large, chronic, fibrotic ulcer is shown, which has perforated. Note that the ulcer is in the jejunum immediately opposite the stoma and that there is a margin of normal jejunal mucosa between the ulcer and the anastomotic suture line. Also note that in the anastomotic suture line opposite the ulcer there are two black silk sutures lying free, but no associated ulcer.

operation, already presented a typical chronic ulcer with a dense fibrotic base. This ulcer microscopically revealed evidence of healing by the encroaching tongue of epithelium over the fibrotic base. The remaining three dogs had characteristic subacute and chronic ulcer with a hemorrhagic base and gross evidence of hemorrhage in the gastro-intestinal tract.

Of pertinent interest is the unusual finding of black silk sutures lying free in the base of the anastomotic ulcer in two of the dogs (fig. 11). As in all the operations, no. 00 chromic catgut was used for the hemostatic suture and black silk for the seromuscular suture. This associated occurrence of ulcer is in direct contrast to the observations of Hosoi,[65] in which loose threads were found hanging in the lumen but with no evidence of associated ulceration in six instances. This contradictory finding will be discussed later.

Of the eighteen animals in which ulcer developed, thirteen showed a single ulcer and five had two ulcers. Thus, in this group there was only a slight increase of approximately 8 per cent over the 20 per cent incidence of multiple ulcers in

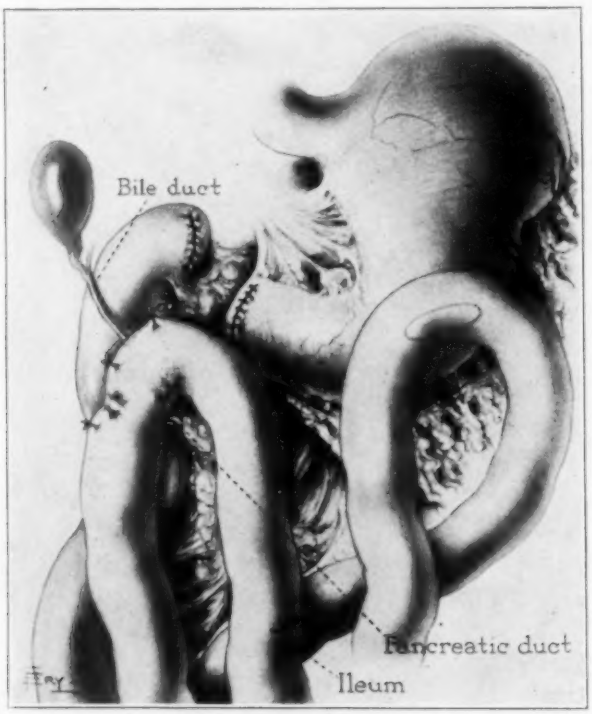

Fig. 12.—Drawing of the completed operative procedure performed on group 4. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The accessory pancreatic duct was ligated and severed. The main pancreatic duct and the common bile duct were transplanted into the terminal portion of the ileum.

group 1. The ulcers varied in size from 0.4 to 1.5 cm. in diameter. They were usually round or oval, with characteristic indurated, overhanging margins or with some undermining of the edges. Analysis of the site of the ulcers reveals some interesting facts. In thirteen of the eighteen dogs in which ulcer occurred the location was in the efferent loop of the jejunum, as in group 1. In six of the

65. Hosoi, K.: Peptic Ulceration: Its Relationship to Gastro-Intestinal Chemism, Thesis, 1934.

eighteen dogs (33.3 per cent) the ulcer was situated in the jejunum directly opposite the stoma, usually on the antimesenteric side (figs. 2 and 11). Of the six, there were two in which two ulcers were present, in each of which the other ulcer occurred in the efferent loop of the jejunum, as in group 1. In four of the eighteen dogs (22.2 per cent) an anastomotic ulcer was present in the suture line, with loose black silk hanging from the base in two instances. In two of these four animals there was another ulcer in the jejunum opposite the stoma in one and in the efferent loop of the jejunum in the other. In no instance was an ulcer found in the afferent loop of the jejunum. One dog, dying of a perforated ulcer and peritonitis fifty-seven days after operation, demonstrated the development of a biliary calculus. At the opening of the transplanted common bile duct into the wall of the terminal portion of the ileum there was present one of the black silk sutures, and on its end there was a round dark brown biliary calculus.

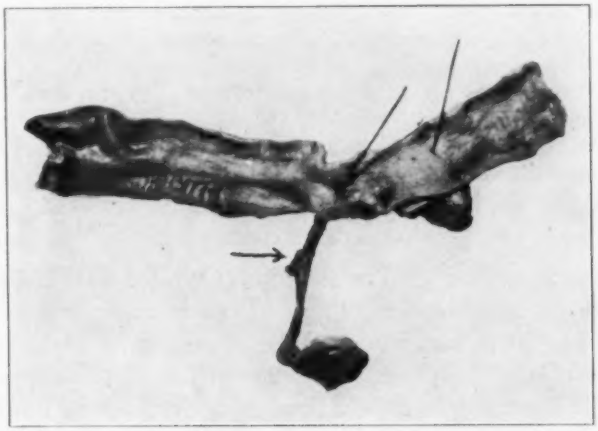

Fig. 13.—Photograph of the opened terminal portion of the ileum with straws passing through the opening of the transplanted pancreatic and common bile ducts. The arrow points to the end of the straw, showing through the opening made in the common bile duct.

GROUP 4.—*Pyloric Occlusion, Gastrojejunostomy and Deviation of Bile and Pancreatic Juice.*

Method.—The same procedure as that used on group 1 was performed, but in addition both the common bile duct and the main pancreatic duct were transplanted into the terminal portion of the ileum (fig. 12). The same technic was used for transplanting the ducts as was used for groups 2 and 3, respectively. The common bile duct was transplanted approximately 5 cm. above the pancreatic duct (fig. 13). The small accessory pancreatic duct was always sought and if identified was severed and ligated so that no pancreatic juice entered the duodenum. At autopsy it was definitely determined that no pancreatic juice had entered the duodenum. The foregoing surgical procedure rarely required more than one hour and thirty minutes and was frequently performed in sixty or seventy minutes.

Results.—This group consisted of ten dogs, which lived from twelve to fifty-one days after operation. Although the animals had a rapid immediate recuperation from the operation, they rarely maintained a normal appetite and weight except for a short time. In the majority of instances, after about the second post-

operative week they began to evince anorexia, rapid loss in weight and general decline, with marked weakness and apathy. The shortest postoperative duration was twelve days, the longest fifty-one days and the average about twenty-five days, or three and a half weeks.

Ulceration occurred in all the animals. This was complicated by perforation with resulting peritonitis in five, or 50 per cent. In one dog, which died of pneumonia seventeen days after operation, a chronic ulcer had already developed. In four instances the ulcers were subacute and chronic, with marked gastro-intestinal hemorrhage. Whereas in group 2 there was an incidence of multiple ulcer of 57 per cent, in this group there was an incidence of only 20 per cent. The ulcers varied in size from 0.4 to 2.5 cm. in diameter.

Here again there is a slight variability in the location of the ulcers although not as pronounced as in group 2. In two dogs, dying fifty-one and twenty-one days, respectively, after the operation, a chronic ulcer was found in the afferent loop of the jejenum. In the dog dying twenty-one days after operation there was another ulcer in the jejunum on the efferent side of the stoma which had perforated. In the dog dying fifty-one days after operation only one ulcer was present, and this was of the chronic type. In nine of the ten dogs the ulcer was in the efferent loop of the jejenum, and in one of these there were three ulcers present successively, alined with about 0.5 cm. of normal mucosa separating them. There was no anastomotic ulcer in any of the dogs.

COMMENT

The basic procedure used on the four groups of dogs is nothing more or less than the von Eiselberg [66] type of operation, in which the pylorus is sectioned and the gastric and duodenal ends closed with reestablishment of continuity by gastrojejunostomy (fig. 7). This was all that was done on the first group of animals, but for each of the other three groups there was one added change, i.e., the deviation of pancreatic juice in the second group, the deviation of bile in the third and the deviation of both pancreatic juice and bile in the fourth group. Thus any difference in results obtained in each group may be accounted for by the added change.

Of the first group of twenty dogs, in which pyloric occlusion and gastrojejunostomy alone were performed, jejunal ulcer developed in 50 per cent. This is a slightly higher incidence than is usually reported and is worthy of some consideration. Why should ulcer develop at all after this procedure? The physiology of the gastro-intestinal tract does not seem to be altered to such a commensurable degree. There is no deviation of alkaline juices. The gastric acidity should not be increased. It would appear that the best possible explanation is that the jejunal mucosa is functionally unable to receive acid gastric chyme, and this factor is relatively more pronounced after this procedure, as the pyloric occlusion does not permit a regurgitation of the alkaline duodenal juices into the stomach to help neutralize the gastric acidity. However,

66. von Eiselberg, quoted by Alvarez.[1h]

it must be remembered that the latter factor is debatable. Ivy and Fauley [67] have clearly demonstrated the differences existing between the duodenal and the jejunal mucosa in their respective abilities to cope with acid gastric chyme. They performed the "surgical duodenal drainage" operation, which was modified by leaving an inch or so of duodenum attached to the pyloric end of the stomach. Ulcer always developed in the jejunal mucosa, although the duodenal mucosa was subjected to the same force of impinging gastric juice. Of course, in the procedure under consideration the traumatic factor (Mann and Williamson; McCann) of the propulsive nozzle-like action is certainly minimized, and it is necessary to resort to the chemical theory and the lessened resistance of the jejunal mucosa to explain the high incidence of the occurrence of ulcer.

Another interesting factor revealed by this series of experiments is the characteristic site of the ulcer, i. e., in the efferent loop of the jejunum. This seems to confirm the theory of acidity. The afferent loop is to a certain extent protected by the alkaline duodenal juices, as in their passage downward they reach the afferent side of the anastomosis first and exert the greatest degree of neutralizing power. However, after passing the stoma they lose to a great extent this acid-neutralizing power, and the jejunal mucosa of the efferent loop is exposed to acid gastric chyme of relatively higher acidity.

The incidence of ulcer formation here (50 per cent) is apparently somewhat higher than is usually reported. Alvarez [1h] reported a general incidence of 25 per cent. Clinical reports of incidence reveal a marked variance of from 1 to 2 per cent (Moynihan [68]) to as high as 52 per cent (Hurst and Stewart [69]). According to Lewisohn,[70] Lamson [71] and Strauss, Bloch and Friedman,[72] an incidence varying from 2.5 to 34 per cent has been reported. Of course, these incidences are not quite comparable, as the procedure in these instances does not usually entail pyloric occlusion, and the subject operated on is not normal. Nevertheless, an incidence of from 25 to 50 per cent is to be expected, and the number observed here is not altogether out of proportion.

Of the second group of ten dogs, in which an operation similar to that used on the animals in group 1 was performed but with the addi-

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67. Fauley, G. B., and Ivy, A. C.: Experimental Jejunal Ulcer, Proc. Soc. Exper. Biol. & Med. **27**:182, 1929. Footnote 36.

68. Moynihan, B.: Treatment of Duodenal Ulcers, Lancet **1**:631, 1923.

69. Hurst, A. F., and Stewart, M. J.: Jejunal and Gastrojejunal Ulcers, Lancet **2**:742, 1928.

70. Lewisohn, R.: Frequency of Gastrojejunal Ulcers, Surg., Gynec. & Obst. **40**:70, 1925.

71. Lamson, O. F.: Gastrojejunal Ulcer, S. Clin. North America **13**:95, 1933.

72. Strauss, E. E.; Bloch, L., and Friedman, J. G.: Gastrojejunal Ulcer: Medical and Surgical Considerations, J. A. M. A. **90**:181 (Jan. 21) 1928.

tion of deviation of the pancreatic juice into the terminal portion of the ileum, typical subacute and chronic ulcer developed in seven animals (70 per cent). The factors involved in the experiment on this group are exactly similar to those involved in the experiment on group 1, except that there was a deviation of pancreatic juice, so that there were only two alkaline duodenal juices remaining to protect the jejunum, viz., succus entericus and bile. A mathematical comparison revealed that ulcer occurred in a 20 per cent higher incidence in group 2 than in group 1. In other words, deviation of pancreatic juice produced ulcer in 20 per cent of instances, which indirectly indicates its protective influence against the formation of ulcer. This is slightly in contrast to the observations made by Neumann, Deloyers and de Moor [73] and Berg and Jobling.[53] These findings are somewhat in agreement with those of Elman and Hartmann,[56] who found ulcer in each of six dogs in which there was a continued loss of total pancreatic juice. On the other hand, Neumann, Deloyers and de Moor [73] and Berg and Jobling [53] found that pancreatic juice exerted little, if any, protective influence against ulcer formation. The results obtained in my experiments fall between these two extremes. Pancreatic juice undoubtedly plays a definite protective rôle in the prevention of the formation of peptic ulcer, and the 20 per cent higher incidence of ulceration in this group as compared with the incidence in group 1 irrefutably justifies this statement. Besides the ulceration which occurred at the usual sites in the efferent loop of the jejunum, it was present in the anastomotic line, in the jejunum opposite the stoma and in one instance in the efferent loop. In the dogs in the first group in which there was no deviation of the alkaline duodenal juices, ulcer occurred in a characteristic site, i. e., the efferent loop of the jejunum. Ulcer never occurred in the more unusual sites, such as the afferent loop of the jejunum, the anastomotic suture line and the jejunum opposite the stoma. These unusual sites are proximal to the usual sites, i. e., the efferent loop of the jejunum.

Of the third group of twenty dogs, in which an operation similar to that used on group 1 was performed but with the addition of deviation of bile into the terminal portion of the ileum, typical subacute chronic ulcer developed in eighteen, an incidence of 90 per cent. Here again, all the factors involved in the experiment on group 1 apply, except the deviation of the pancreatic juice. In this group the incidence of ulcer was 40 per cent higher than the incidence in group 1 (fig. 5). The procedures used on the two groups of animals were the same, with the exception that in group 3 bile was excluded from the anastomotic site. It is therefore apparent that the bile exerts a protective influence on the jejunal mucosa as regards the formation of ulcer when this is exposed to acid gastric chyme. In other words, deviation of bile pro-

73. Neumann, Deloyers and de Moor, footnotes 26 and 55.

duced ulcer in 40 per cent of instances, which indirectly indicates its protective influence against the formation of ulcer. This is in accordance with the results obtained by Kapsinow [59] and Neumann, de Moor and Deloyers.[55] That bile is probably the most influential constituent of the alkaline duodenal juices has been the opinion of the majority of experimental investigators.

Of particular interest in this group is the occurrence in two of the dogs of black silk sutures hanging free in the base of the anastomotic ulcer. Suture material was used only on the outside row of the seromuscular suture. Judd [74] reported nonabsorbable suture material still present in the ulcer in nine of fifty-five cases, or 16.25 per cent, in which the operation had originally been performed at the Mayo Clinic, and in seventeen of forty-six cases in which gastrojejunostomy had been performed elsewhere. Valdoni [75] observed sixty-one peptic ulcers postoperatively, of which six had old silk sutures lying loose at the bottom of the ulcer. He subsequently made an experimental study on dogs to determine the mechanical effect of nonabsorbable suture material and concluded that it is an important local predisposing cause of a postoperative ulcer. Walton [76] recorded nine of twenty cases in which a portion of suture was present at the base of the ulcer. On the other hand, Sistrunk [77] and Moynihan [68] reported cases in which suture material was found hanging from the stoma for many years with no ulceration. Hosoi,[65] in experimental observation on fifty-seven dogs, noted black silk suture hanging free from the suture line in six instances, with no evidence of anastomotic ulceration. Lewisohn [70] expressed the belief that the type of suture material used is not important. In all probability the tendency has been to stress this factor unduly. It will be observed that there were six of the eighteen ulcers (33.3 per cent) that occurred in the jejunum immediately opposite the stoma. There were also four anastomotic ulcers (22.2 per cent), and two of these contained pieces of bright silk thread hanging free from the base. The presence of these ulcers in as high an incidence as 33.3 and 22.2 per cent, respectively, demands some explanation. Neither type of ulcer was present in group 1. Undoubtedly the explanation is to be found in the chemical theory, as it is impossible to overlook the fact that the only difference between the dogs in group 1 and those in group 2 is the absence of bile in the latter. Ulceration occurred more readily in the latter group because there was an absence of an influential and undeniably effective acid-neutralizing agent. Although in the anasto-

74. Judd, E. S.: Jejunal Ulcer, Surg., Gynec. & Obst. **33**:120, 1921.

75. Valdoni, P.: Relation Between Postoperative Ulcer and Presence of Threads of Silk on Neostomy, Policlinico (sez. chir.) **39**:571, 1932.

76. Walton, A. G.: Gastrojejunal Ulcer, Lancet **2**:800, 1925.

77. Sistrunk, quoted by Hurst and Stewart.[69]

motic ulcer there was present a chronically irritating and traumatic factor in the nonabsorbable suture material, it became sufficiently pronounced to produce ulcers only when there was the added influence of inadequate neutralizing power of the alkaline duodenal secretion. That bile has a greater protective influence than pancreatic juice in preventing the development of ulcer is clearly demonstrated by the comparative incidences of ulcer in group 3 (90 per cent) and group 2 (70 per cent). This induces me to concur with the opinions of Berg, Johnston and Jobling [62] that bile exerts a greater protective influence than pancreatic juice in the prevention of the formation of peptic ulcer and to disagree with Elman and Hartmann and their associates,[57] who opine that the protective power of pancreatic juice is greater. On the other hand, I cannot agree with the opinion of the former investigators, that pancreatic juice is of little or no importance in the prevention of ulcer, or with the view of the latter, that bile is of little or no consequence.

In group 1, in which there was no deviation of the alkaline duodenal juices, ulcer occurred in a characteristic site, i. e., the efferent loop of the jejunum. Ulcer never occurred in the more unusual sites, such as the afferent loop of the jejunum, the anastomotic suture line and the jejunum opposite the stoma. These unusual sites are proximal to the usual sites, i. e., the efferent loop of the jejunum. The occurrence of ulcer in these more proximal locations occurred only when one of the alkaline juices, bile or pancreatic juice, was deviated, thus indicating that under these circumstances there is a less adequate neutralization of acid gastric chyme. The fact that they occurred more frequently in group 3 (deviation of bile) than in group 2 (deviation of pancreatic juice) indicates that bile exerts a greater acid-neutralizing power.

If the protective influence of bile and pancreatic juice is attributed to their alkalinity or their acid-neutralizing powers, the correlation of the findings of Jones [78] becomes interesting. This author aseptically collected bile and pancreatic juice from five dogs, titrated twenty-four hour specimens with tenth-normal hydrochloric acid and determined the p_H with a quinhydrone electrode. He observed that pancreatic juice was usually more alkaline (p_H from 7.8 to 9) than hepatic bile (p_H from 7.4 to 8.5). However, he stated that hepatic bile may be as alkaline as pancreatic juice, as the two act in a compensatory manner, but that the amount of pancreatic juice secreted is more than that of bile when both are flowing freely. He also found that the buffer action is due to sodium bicarbonate, a substance common to both secretions. Boldyreff [30] found bile from the gallbladder to have a percentage of alkalinity (sodium carbonate, Na_2Co_3) of 0.05, as compared with that of pancreatic juice, 0.65.

78. Jones, K. K.: Comparison of Buffer Value of Bile and Pancreatic Juice Secreted Simultaneously, Proc. Soc. Exper. Biol. & Med. **28**:567, 1931.

In the fourth group there were ten dogs, in which an operation similar to that used on group 1 was performed except that the pancreatic and common bile ducts were both transplanted into the terminal portion of the ileum. In this procedure there was only the duodenal secretion to protect the sensitive jejunal mucosa. There was an incidence of ulcer of 100 per cent. Such an extremely high incidence indicates complete absence of protective influence. This is in accord with the experience of Mann and Williamson,[6] Mann and Kawamura [42] and Grey,[43] who performed duodenectomy and concluded that the duodenum is apparently not essential to life. It would appear that the combined elimination of bile and pancreatic juice will result in a higher incidence of ulcer than their elimination singly or the exclusion of one or the other in combination with the duodenal secretion. This is in contrast to the opinion of Bauer and Aron,[41] who maintained that duodenal secretions exerted the greatest protective influence.

It will be noted that in this group there were no anastomotic ulcers, and in only one animal was there an ulcer only in the afferent loop. This is not in accord with the findings in groups 2 and 3. From the results in the latter groups, a higher incidence of ulcer at these unusual sites would be expected. The only explanation that can be offered for this is that possibly the dogs died sooner and as a result ulcer did not have time to develop, as it will be noticed that the average postoperative period for these dogs was twenty-five days as compared with forty-two days and thirty-four and six-tenths days for the animals in groups 2 and 3, respectively. It must be admitted, however, that it is a rather weak explanation.

GENERAL SUMMARY AND CONCLUSIONS

A review of the voluminous literature which has now accumulated on the relative protective value of the alkaline duodenal juices in preventing the formation of ulcer has served to give some comprehension of the bewildering maze of confusion that now exists. It has been suggested that this diversity of opinion and the contradictory experimental results have been due in great measure to the fact that observations and comparisons have been made by different investigators under varied and different circumstances. Because of the present day difficulty in drawing conclusions from the confused and risibly contradictory experimental results, this investigation was made. The experiments were performed in such a manner as to permit without criticism the drawing of conclusions from the results obtained. The dogs used in the investigation were divided into four groups. In the first group the pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The same procedure was performed on the second group, but with the addi-

tion of ligation and division of the accessory pancreatic duct and transplantation of the main pancreatic duct into the terminal portion of the ileum. The third group of animals was subjected to the same procedure as the animals in first group, but with the addition of transplantation of the common bile duct into the terminal portion of the ileum. The fourth group was also subjected to the same procedure as the first, but with the addition of transplantation of both the bile and the pancreatic duct into the terminal portion of the ileum. Obviously the procedures used on all the animals are similar with the exception of one factor, the deviation of pancreatic juice in the second group, the deviation of bile in the third, and the deviation of both bile and pancreatic juice in the last group. Thus, because of the excellent comparability of the procedures used on the four groups any difference in results obtained can be accounted for by the one different factor characterizing each experiment. In this manner more convincing conclusions can be drawn.

A total of sixty dogs was used in the four groups. Twenty animals were used in the first group, ten in the second, twenty in the third and ten in the fourth. In the first group, which served as controls, the basic operative procedure performed consisted of severance of the pylorus with closure of both ends and anterior gastrojejunostomy. The twenty dogs operated on lived from nine to two hundred and seventy-one days, and subacute and chronic ulcer developed in ten, an incidence of 50 per cent. In the ten dogs in which ulcer developed, perforation and peritonitis occurred in seven. The ulcers were grossly and microscopically similar to ulcers occurring in man. All the ulcers developed at a characteristic site, i. e., in the jejunal mucosa of the efferent loop. The explanation for this high incidence of ulcer after this procedure and the characteristic location is that the jejunal mucosa has little resistance to the acid gastric chyme, and the efferent loop of the jejunum is bathed with gastric chyme of relatively higher acidity than the efferent loop or the jejunal mucosa immediately opposite the stoma.

The same operative procedure was performed on the second group of dogs as on the first group, except that the main pancreatic duct was transplanted into the terminal portion of the ileum, and the accessory pancreatic duct was sought and if found severed and ligated. In this group of ten dogs the incidence of ulcer was 70 per cent. Except for the deviation of the pancreatic juice in this group, all other factors were equal to those involved in the experiment on group 1, yet ulcer developed in the former in a 20 per cent higher incidence than in the latter. This difference in results obtained in these two groups must be accounted for by the only different factor, i. e., the absence of the alkaline pancreatic juice. This seems to justify the conclusion that pancreatic juice exerts a definite protective influence against the formation of jejunal ulcer.

The third group of animals was subjected to the same operative procedure as the first group, except that the common bile duct was transplanted into the terminal portion of the ileum. Of twenty dogs operated on in this group, typical subacute and chronic ulcer developed in eighteen, an incidence of 90 per cent. Except for the deviation of bile in this group, all other factors were equal to those involved in the experiment on group 1, yet ulcer developed in the former in a 40 per cent higher incidence than in the latter. This marked difference in results obtained in the two groups of dogs must be accounted for by the only different factor in the two groups, i. e., the absence of bile in the alkaline duodenal secretions. Another difference in the results obtained in this group is the occurrence of ulcer in the anastomotic suture line in four instances, with pieces of black silk suture hanging free from the base of two. Still another difference is the occurrence of ulcer in the jejunal mucosa immediately opposite the stoma. The high incidence of these ulcers (anastomotic, 22.2 per cent, and opposite the stoma, 33.3 per cent) proximal to the usual site in the efferent loop emphasizes more strongly the acid-neutralizing influence of the bile. As compared to the incidence in group 2, on which the same procedure was performed except that pancreatic juice was deviated instead of bile, there was a 20 per cent greater incidence of ulcer. It will also be observed that in group 3 ulcer occurred in a slightly greater frequency in the more unusual sites (anastomotic suture line and in the jejunum opposite the stoma) than in group 2. These two differences indicate that bile exerts a greater acid-neutralizing power than pancreatic juice.

The fourth group of dogs was subjected to the same operative procedure as the first group, except that the common bile duct and main pancreatic duct were both transplanted into the terminal portion of the ileum. The accessory pancreatic duct was always sought and if found severed and ligated. Of ten dogs operated on, typical subacute and chronic ulcer developed in all. Except for the deviation of bile and pancreatic juice, all the factors, were equal to those pertaining to group 1, yet ulcer developed in a 50 per cent higher incidence. This indicates that the succus entericus has little or no protective influence in the prevention of ulcer.

A graphic representation of a comparison of the results obtained in the four groups is illustrated in figure 5. These results seem to justify the following conclusions: 1. Of all the constituents of the alkaline duodenal juices, bile has the most significant and effective influence in preventing the formation of jejunal ulcer; (2) the duodenal secretion, the succus entericus, is the least important, and (3) the pancreatic juice is midway between the two in this respect.

HISTOLOGIC STUDIES ON THE FATE OF DEEPLY IMPLANTED DERMAL GRAFTS

OBSERVATIONS ON SECTIONS OF IMPLANTS BURIED FROM ONE WEEK TO ONE YEAR

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This series of experiments was conducted to determine the advisability of filling a depression by burying a free section of dermis and fat underneath the skin. Eitner [1] in 1920 described a method of elevating a depression of the face by inserting a free section of deepithelized derma beneath the skin overlying the depression. He reported a case of paraffinoma of the cheek in which a depression resulted from the removal of the paraffinoma. Eitner removed the epidermis from a hairless portion of the abdomen with a Thiersch knife and excised a section of dermis and underlying fat. This he transplanted under the skin of the cheek. He observed the patient for about eight months and reported a completely satisfactory result. He apparently removed the epidermis for the purpose of insuring sterility of his transplant, but in this article he did not mention the possibility of the formation of a cyst. Vilray Blair and J. B. Brown used dermal grafts and described the method to Straatsma, who successfully used the graft to repair saddle nose.[2] Eagleton, Swain and Peer [3] have successfully repaired large depressions in the forehead resulting from the removal of the frontal sinuses and the adjacent frontal bone by inserting a large graft of dermis, fat and fascia lata beneath the scalp. One patient on whom such a procedure was carried out was followed four years and showed no evidence of the formation of a cyst. Such a formation theoretically might occur from the hair follicles, sebaceous glands or sweat glands in the buried section of dermis. We considered it advisable, therefore, to determine experimentally the fate of epithelial derivatives in the dermis before advocating the use of the buried dermal graft. Our previous experience

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1. Eitner, E.: Ueber Unterpolsterung der Gesichtshaut, Med. Klin. **16**: 93 (Jan. 25) 1920.

2. Straatsma, C. R.: Use of the Dermal Graft in the Repair of Small Saddle Defects of the Nose, Arch. Otolaryng. **16**:506 (Oct.) 1932.

3. Eagleton, W. R.; Swain, R., and Peer, L. A.: Unpublished data.

had shown that dermis buried beneath the skin undergoes little reduction in thickness and hence is superior to fat alone, which is greatly reduced through absorption and partial replacement. The bulk of the graft, when desirable, may also be increased by using a number of dermal strips placed one over the other and held together by mattress sutures of plain catgut. This method of repair has achieved little popularity because of the theoretical possibility of the formation of cysts from sweat glands, hair follicles and sebaceous glands in the dermis or from remnants of epidermis incompletely removed from the surface of the dermis.

PREVIOUS EXPERIMENTAL WORK

Many investigators have performed experiments on animals by burying strips of epidermis and full thickness skin. In these experiments cysts were observed originating from the epidermis and from the hair follicles. In man, so far as we know, the investigation has been limited to the observation of traumatic epithelial cysts resulting from injury or following an operative incision. Reverdin [4] expressed the belief that as a result of trauma bits of epidermis were torn off and deposited deeply in the corium and that cysts developed from these implanted grafts.

Garré [5] stated that the implantation of epidermis alone produced a smooth-walled cyst, while in the cyst resulting from implantation of a whole thickness skin graft papillae were also present.

Kaufmann [6] produced a cyst beneath the skin of the cock's comb by making an oval incision deeply through the skin and suturing the margins of the skin together over the oval section. The buried epidermis gradually took on a rounded form and invariably developed into a cyst. The origin of this cyst from the epidermis was evident, because the cock's comb contains no hair follicles or glandular elements to provide another possible source.

Schweninger,[7] in a similar experiment on dogs, produced a subcutaneous cyst by burying a piece of skin below the surface. Some of the cysts so produced contained hairs and sebaceous glands in their walls and fat, cholesterol and epidermal scales within the lumen.

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4. Reverdin, J. L.: Des kystes epidermiques des doigts, Rev. méd. de la Suisse Rom. **7**:121, 1887.

5. Garré, C.: Ueber traumatische Epithelcysten der Finger, Beitr. z. klin. Chir. **11**:524, 1894.

6. Kaufmann, E.: Ueber Enkatarrhaphie von Epithel, Virchows Arch. f. path. Anat. **97**:236, 1884.

7. Schweninger, E.: Beitrag zur experimentellen Erzeugung von Hautgeschwulsten (Atheromen), Charité ann. **11**:642, 1884.

Pels-Leusden [8] suggested another possible origin for the epithelial cyst and supported it by experiments on the ears of rabbits. He made an incision through the skin, using a "sharp knife" to prevent the accidental implantation of epidermis during the operation. He then placed an absorbable magnesium disk deeply within the corium. A cyst was produced about the foreign body, the lining membrane of which contained all the layers of normal epidermis. Pels-Leusden expressed the belief that such a cyst was formed by proliferation from the epithelium of glands that were unavoidably injured by the incision. He thought it unlikely that in an ordinary injury the tough skin of the palm could be torn off and implanted.

Hesse,[9] in a series of experiments, buried a magnesium disk, catgut and a blood clot beneath the skin and later examined histologic serial sections of the sites of implantation. He demonstrated that epithelization to produce a cyst may take place from the hair follicles and glandular epithelium without any apparent burial of epidermis. He was unable to find papillae in the wall of any of the cysts produced, however, and he stated that for the development of papillae the implantation of whole thickness skin was necessary.

Davis and Traut [10] produced epithelium-lined tubes and sacs in dogs by transplanting free whole thickness skin grafts directly onto one of the abdominal muscles. In each animal the fascia was drawn over the graft, and the graft was left in place from twenty to forty days. The animal was killed, and the buried skin with adjacent structures was carefully removed and fixed in formaldehyde. The authors noted the formation of an epithelium-lined tube or cyst resulting from a cylindric growth at the margins of the skin graft. They stated that when the experiments were carried beyond forty days maceration of the epithelial lining of the cavity of the cyst occurred. They assumed that this is due to pressure from the content of the cyst. The fate of hair follicles and glandular elements in the dermis of the skin graft is not histologically described.

Zimches,[11] in a series of his own experiments and in experiments with Wassiljew, buried free strips of full thickness skin in the muscle

8. Pels-Leusden, F.: Ueber abnorme Epithelisierung und traumatische Epithelcysten, Deutsche med. Wchnschr. **31**:1340, 1905.

9. Hesse, F. A.: Die Entstehung der traumatischen Epithelcysten, Beitr. z. klin. Chir. **80**:494, 1912.

10. Davis, J. S., and Traut, H. F.: The Production of Epithelial Lined Tubes and Sacs, J. A. M. A. **86**:339 (Jan. 30) 1926.

11. Zimches, J. L.: The Fate of Surface Epithelium Transplanted into Deeper Tissues and Its Relation to Epithelial Cysts, Frankfurt. Ztschr. f. Path. **42**:203, 1931.

of dogs. His conclusions based on implants buried up to two years were as follows:

(*a*) The epidermis of the implanted skin curves in the shape of a horseshoe, and on about the twenty-fifth day the ends of the horseshoe join, forming a circle or closed cavity lined by epithelium.

(*b*) The cavity of the cyst is partly filled by epithelial débris and broken-down hairs.

(*c*) The cyst continues to grow because the lining epithelium constantly produces cornified epithelium, which is pushed into the lumen.

(*d*) Smaller cysts may develop from the epithelium of hair follicles.

(*e*) The tendency of surface epithelium, when transplanted into other tissue, to bend on itself and form a closed cavity represents a definite law and finds its explanation in the general growth law of epithelium.

(*f*) Changing of one kind of epithelium into another or into malignant tissue was never found in these experiments.

(*g*) The implanted section of skin heals in its new position and quickly joins the surrounding tissue by means of granulation tissue, which is later organized into connective tissue.

The occurrence of foreign body giant cells in the unlined wall of an epidermal cyst has been explained by Stewart.[12] According to him, the contents of the cyst, whether hair, fat, cholesterol or epithelial débris, have the irritant properties of a foreign body. In those parts of the cyst where the epithelial lining is lacking, this irritation produces a type of granulation tissue rich in giant cells.

Wien and Caro [13] stated that the traumatic epithelial cyst is believed to develop as a result of injury to the skin and occurs most frequently on exposed sites, such as the palms and fingers. The probable origin of the cyst is from epidermis torn from the surface and carried into the corium. Such a cyst may also form about a foreign body implanted into the dermis by proliferation of epithelium from the hair follicles or glandular elements of the skin.

The foregoing experiments were conducted on animals and dealt with the production of an epidermal cyst by the transplantation of epidermis into other tissues and with the production of a cyst from hair follicles when a full thickness section of skin was implanted or when a foreign body was introduced into the dermis.

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12. Stewart, M. J.: On the Occurrence of Irritation Giant Cells in Dermoid and Epidermoid Cysts, J. Path. & Bact. **17**:502, 1912.

13. Wien, M. S., and Caro, M. R.: Traumatic Epithelial Cysts of the Skin, J. A. M. A. **102**:197 (Jan. 20) 1934.

Our work was done on human beings. Free sections of skin and fat from which the epidermis had apparently been removed were buried beneath the skin of the chest and removed for histologic examination at intervals of from seven days to twelve months. These experiments were possible because of the large number of rib graft operations performed in our service at the Newark Eye and Ear Infirmary. When a rib graft operation for saddle nose is done, the excess portion of the rib cartilage is stored beneath the skin of the chest for future use in case the nasal graft becomes infected. If infection does not develop, the rib cartilage in the wall of the chest is removed and scrapped. Hence in our experiments it was possible to insert free sections of dermis and fat beneath the skin of the chest together with the rib cartilage and remove them at various intervals following successful operation on the nose.

EXPERIMENTAL PROCEDURE

A free elliptic section of skin and subcutaneous fat was removed from the abdomen of a number of patients on whom a rib graft operation was performed for the repair of saddle nose. The epidermis was shaved from each section as completely as possible with a sharp no. 11 Bard-Parker knife blade, and the remaining dermis and fat were inserted beneath the skin of the chest with the dermis outermost. At intervals of seven days, fourteen days, twenty-one days and two months, seven months and twelve months each impant was excised together with the overlying skin of the chest and placed in Zenker's solution. After an implant was sectioned in the usual manner, the tissues were stained with hematoxylin and eosin, and after examination they were photographed under high and low power magnification.

DESCRIPTION OF SECTIONS

The sections here described were prepared by Mr. David J. McKinnon, of the Newark Eye and Ear Infirmary. They represent various stages of the transplanted dermis from the abdomen.

Six stages are represented, as follows: one week, two weeks, three weeks, two months, seven months and one year. The most striking feature in the sections was the persistence of the apparently removed epidermis, which was definitely present in the four earlier sections and may have been present in the two later sections. The latter showed certain features which might indicate a temporary persistence of the epidermis.

The next observation which struck the eye was the difference in behavior between the two kinds of glands present in the dermal implant. The only surviving sebaceous gland was found in the section of the implant buried for one week; none was discovered in any of the later sections. On the other hand, the sweat glands were apparent in the implants of all stages, although the later sections showed them to be considerably changed.

The other striking observation concerns the reaction of the subcutaneous connective tissue of the site of the chest to the dermal implant. This was most pronounced in the middle stages but was found in some degree in all stages. It was a chronic inflammatory reaction of the granulomatous type, with the formation of granulation tissue containing beside the usual young capillaries and young fibroblasts, a large number of mononuclear cells and their derivatives. These are lymphocytes, macrophages and epithelioid or endothelioid cells (these both differing from macrophages mainly in being closely packed together) and giant cells.[14] The last, although large multinuclear cells, are believed to be derivatives of the mononuclear epithelioid cells. These cells were either diffusely arranged or distributed in the form of granulomatous nodules of microscopic size containing all the aforementioned types of mononuclear cells, together with foreign bodies,

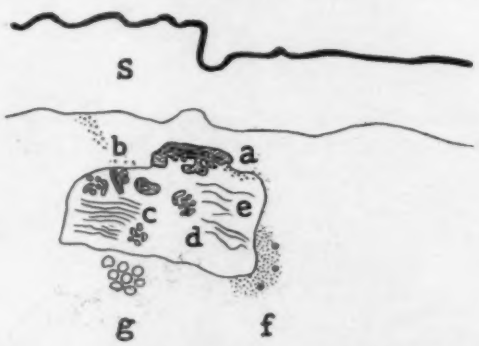

Fig. 1.—Diagram of a dermal implant at one week. *S* indicates the overlying skin of the chest; *a*, a flat epithelial cyst; *b*, a hair follicle with a sebaceous cyst; *c*, an empty hair follicle; *d*, sweat gland tubules; *e*, collagenous fibers of the implant; *f*, granulation tissue, and *g*, fat.

to be later described, the whole being surrounded by a fibrous capsule.[15] The cause of this type of reaction, we believe, is particulate in nature and organic in chemical composition, but not microbic.

In the first section (figs. 1 and 2) we found the rather square rectangular implant well demarcated from the surrounding tissue, lying a little below the overlying skin. Immediately beneath the area of the incision, at the upper border of the implant, there was a small flat epithelial cyst or cleft (fig. 3). On its lower surface the papillae were well marked, the epidermis showing marked irregularity along its lower border and a cross-section of a hair follicle. The upper border, although showing almost as many layers of stratified squamous epithelium, presented no processes and showed no papillae along its outer border. The epithelial cyst or cleft contained some thin plates of horny material.

14. A similar type of cellular reaction was found by Zimches after implantation of dog's skin into muscle.

15. The granulomatous nodule is not mentioned by Zimches, only the diffuse type of cellular reaction.

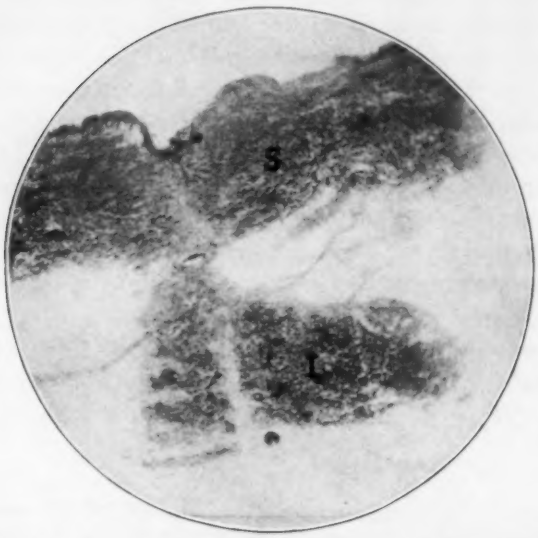

Fig. 2.—Section of a dermal implant at one week, showing the location beneath the skin of the chest; × 10. *S* indicates the skin of the chest, and *I*, the dermal implant.

Fig. 3.—Section of a dermal implant at one week, showing a flat epithelial cyst, originating from the epidermis of the implant; × 100. The cavity of the cyst is indicated by *a*, the epithelium lining cyst by *b*, the papillae beneath the epithelium of the floor of the cyst by *c* and a hair follicle, cut across, by *d*.

The foregoing observations are considered as determining that the epithelial cyst or cleft has developed from a small area of epithelium inadvertently left on the dermal implant. The presence of well marked papillae along the lower border is the criterion, since it is generally held, as previously mentioned, that papillae do not develop under regenerated epithelium. We concluded, therefore, that the epithelial cleft or cyst developed from the epidermis of the implant.

To the left and below the epithelial cleft there was a small oval epithelial island with a small cavity and rather thick walls of stratified squamous epithelium. The cavity contained no hair or horny material.

In one area of the implant, along the upper border, a hair root with its follicle and a definite sebaceous gland was found (fig. 4). The cells of the gland were not well preserved, suggesting that it was already deteriorating. This assumption is borne out by the fact that no sebaceous glands were found in the later sections, although such negative evidence cannot be taken as finally conclusive.

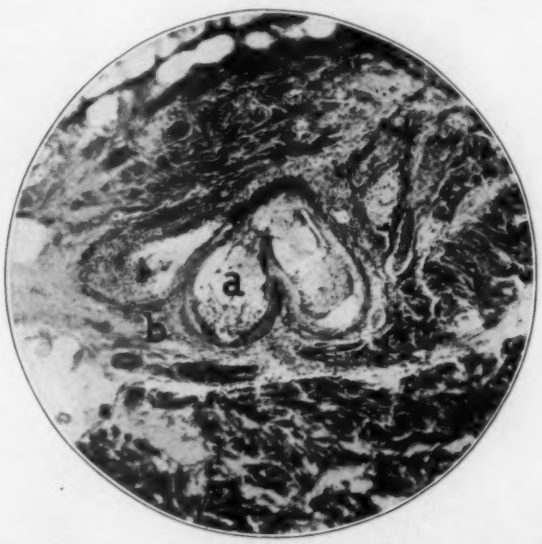

Fig. 4.—Section of a dermal implant at one week, showing a surviving sebaceous gland with a hair follicle; × 100. The sebaceous gland is indicated by *a* and the hair follicle by *b*.

Scattered throughout the dense collagenous fibers of the dermis were numerous well preserved sweat gland tubules (fig. 5). There was no apparent increase in the fibroblasts of the dermis.

Beneath and to each side of the implant was found the normal adipose subcutaneous connective tissue. This was not everywhere present in contact with the implant. In certain regions its place was taken by granulation tissue. One strand of this tissue connected the upper border of the implant with the overlying skin. On the lower right corner of the implant the granulation tissue contained a number of giant cells. This tissue will be described more fully in later sections.

The section of the implant buried for two weeks was similar to that of the implant buried for one week in its relation to the overlying skin (fig. 6). In form

it represented an elongate rectangle bent downward at both ends. It showed no epithelial cyst, but near its upper border toward the left there was a small solid island of epithelium evidently derived from the dermal implant (fig. 7). In this island the cells were arranged in orderly fashion, with the basal layer cylindric. There was no horny layer or other layers to be differentiated. The cells appeared healthy and normal. The only other cells of epithelial derivation observed in this implant were those of the fairly numerous tubules of the sweat glands, some of which were not so well preserved as in the previous section, being thinner and poorly stained, though normal in relation to surrounding tissue.

The dense connective tissue of the dermal implant appeared normal. This implant showed a few deeply placed collagenous fibers surrounded by granulation tissue.

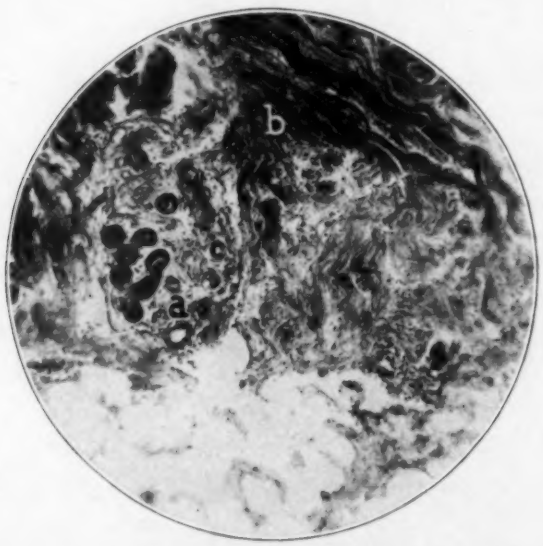

Fig. 5.—Section of a dermal implant at one week, showing the surviving sweat gland tubules of the implant; × 100. The sweat gland tubules are indicated by *a* and the collagenous fibers of the implant by *b*.

The section showed a marked increase in the granulomatous reaction of the connective tissue (fig. 6*e*). The implant was practically surrounded by fresh granulation tissue, containing numerous diffusely distributed lymphocytes, macrophages, epithelioid cells and a considerable number of giant cells. The granulation tissue was most dense and the giant cells most numerous at the upper left angle of the implant. A thick strand of young connective tissue connected the upper surface of the implant with the overlying skin. Another area of the same mononuclear type of granulation tissue adhered to the right margin of the implant and a deep strand ran below, between which and the lower border of the implant normal adipose connective tissue, probably belonging to the implant, was seen. Such adipose tissue, probably belonging to the site of implantation, was seen above the implant, between it and the skin.

In the section of the implant buried for three weeks the implant was situated nearer to the overlying skin, being separated only by a narrow area filled with young fibrous and granulomatous tissue (fig. 8). On the upper left margin it was separated definitely from the overlying skin by the normal subcutaneous adipose

Fig. 6.—Diagram of a dermal implant at two weeks. *S* indicates the overlying skin of the chest; *a*, the epithelial island, originating from the epithelium of the implant; *b*, the sweat gland tubules; *c*, the collagenous fibers of the implant; *d*, fat, and *e*, granulation tissue surrounding the implant, containing giant cells.

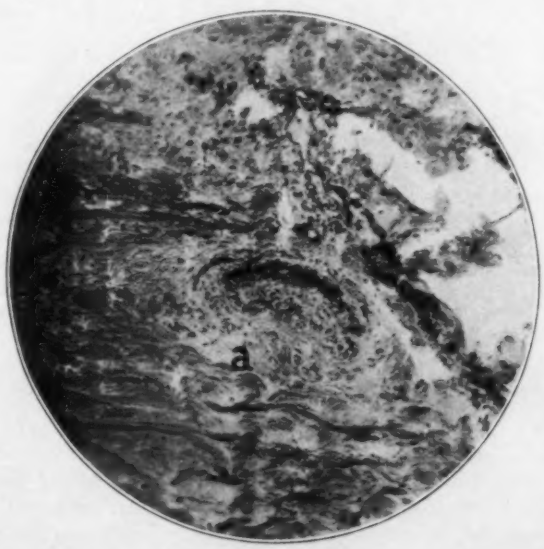

Fig. 7.—Section of a dermal implant at two weeks, showing an epithelial island (*a*), originating from the epidermis of the implant; × 100.

layer. In this region the upper border of the implant showed a definite and comparatively large flat oval epithelial cyst (fig. 9). The lower border showed papillae with one long sharp process of epithelium extending downward from the basal

layer. The cavity of the cyst was flat and contained horny material. The upper wall of the cyst was smooth and showed no papillae at its outer margin.

At about the same level, close to the upper margin, there was an elongate hair follicle containing its hair root cut in diagonal section. Space existed between the hair and the follicle cells, which was partly filled with horny material. Farther

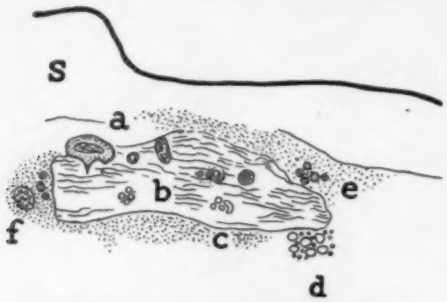

Fig. 8.—Diagram of a dermal implant at three weeks. An epithelial cyst, containing horny material is indicated by *a;* hair follicles, one of which is forming a small cyst, by *b;* sweat gland tubules by *c;* fat, in process of replacement by mononuclear cells, by *d;* granulation tissue, containing giant cells, surrounding the implant, by *e,* and a granulomatous nodule by *f.*

Fig. 9.—Section of a dermal implant at three weeks, showing an epithelial cyst derived from the epidermis of the implant; × 100. The cavity of the cyst, containing horny material, is indicated by *a,* the epithelium lining the cyst by *b* and the papilla beneath the epithelium of the floor of the cyst by *c.*

to the right there was a round hair follicle, cut in transverse section (fig. 10). It showed a similar space between the wall of the follicle and the enclosed hair root, with horny material in it. Another follicle in this section showed the beginning formation of a cyst (fig. 11).

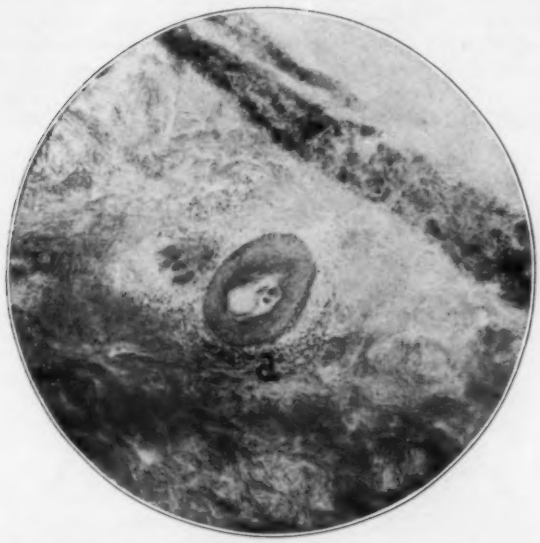

Fig. 10.—Section of a dermal implant at three weeks, showing a surviving hair follicle (*a*) of the implant; × 100.

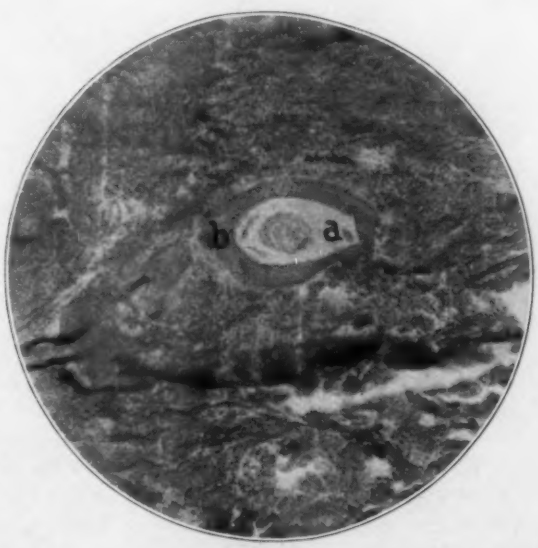

Fig. 11.—Section of a dermal implant at three weeks, showing a hair follicle in the implant and beginning formation of a microscopic cyst; × 100. The cavity of the cyst, containing centrally placed horny material, is indicated by *a* and the epithelium of the hair follicle lining the cavity of the microscopic cyst by *b*.

Sweat glands were present in this implant, but they showed degenerative changes. They were thinner, stained poorly and were invaded by mononuclear cells (macrophages).

One of the most marked features of this section was the marked response of the connective tissue of the site of implantation. The implant was practically surrounded with young connective tissue, which in places contained many lymphocytes, macrophages and endothelioid cells. In two regions there were definite accumulations of giant cells—near the upper right angle and adjacent to the left margin. Here there was a marked accumulation of granulation tissue with a number of giant cells, and in one area a definitely outlined granulomatous nodule or large oval accumulation of closely packed epithelioid cells and lymphocytes with a fibrous capsule.

In the few areas where adipose tissue was in contact with the lower margin of the implant, the fat cells had been invaded by large mononuclear cells, which

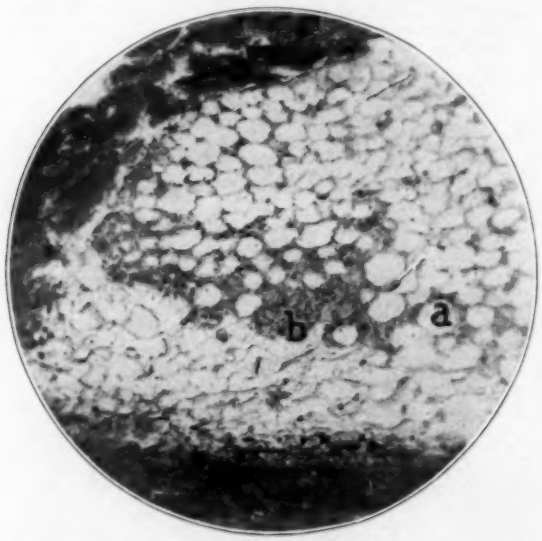

Fig. 12.—Section of a dermal implant at three weeks, showing the subcutaneous fat tissue of the implant in the process of change to tissue of chronic inflammatory type; × 100. The fat cell is indicated by *a* and the area showing replacement by mononuclear cells (macrophages) by *b*.

filled the spaces between the fat droplets, apparently replacing the fat globules and changing the adipose tissue into tissue of the chronic inflammatory type (fig. 12).

The next section represented a considerably later stage of the subcutaneously implanted dermis (fig. 13). It was obtained after two months of implantation. The implant lay at an angle with the overlying skin, its left border in contact with the deeper layers.

Along the slanting upper border of the implant, which was rather clearly defined, there was a sharply defined layer of epithelium bent on itself at the lower border, forming a sharp-angled fish-hook, with the point turned upward toward the overlying skin (fig. 14). In the cavity of the angle could be seen plainly the concentrically arranged layers of the cast-off horny layer, as well as a number of remnants of hair (fig. 15). The roof of the cavity of this partly epithelized

cyst, where epithelium was lacking, was formed from a granulation tissue with a fairly well defined border. It contained numerous lymphocytes, macrophages, epithelioid cells and giant cells. Many of the epithelioid cells and giant cells were markedly vacuolated. There was one large hair fragment embedded in this tissue. This granulation tissue extended to the left above and in contact with the bent epithelial process which formed the epithelized portion of the roof. To the right

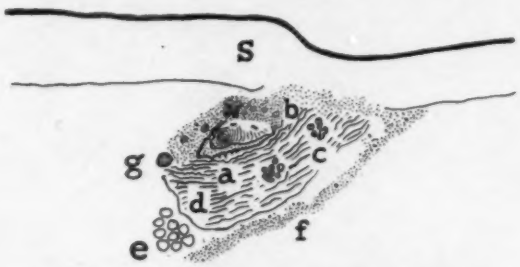

Fig. 13.—Diagram of a dermal implant at two months. *S* indicates the overlying skin of the chest; *a*, a cyst partly lined with epithelium, containing horny material and fragments of hair; *b*, granulation tissue, containing giant cells, forming the roof of the partly lined cyst; *c*, surviving sweat gland tubules; *d*, collagenous fibers of the implant; *e*, fat; *f*, granulation tissue surrounding the implant, and *g*, a granulomatous nodule.

Fig. 14.—Section of a dermal implant at two months, showing an epithelial cyst partly lined with epithelium derived from the epidermis of the implant; × 100. The cavity of the cyst, containing horny material, is indicated by *a;* the epithelium lining the roof of the cyst by *b;* a portion of the roof of the cyst, formed by granulation tissue of the chronic type, containing giant cells, by *c*, and papillae beneath the epithelium of the floor of the cyst by *d*.

it fastened the border of the implant rather firmly to the skin. The other features of this implant were similar to those of the previous sections—persistence of sweat glands with no hair follicles here and a line of granulation tissue extending along the lower border of the implant.

At the left border of the zone of granulation tissue, a little beyond the epithelial margin, there was a small but well defined granulomatous nodule containing the usual elements (figs. 16 and 17).

The two final stages of the implant were observed after seven months and one year of implantation, respectively. They were both characterized by a lack of persistence of the epidermal epithelium, if any were implanted, but showed signs which possibly were to be accounted for by the former presence of epithelium, of the epidermis.

In the section of the implant buried for seven months the implant lay separate from the overlying skin, and at an angle with it (fig. 18). On its upper border

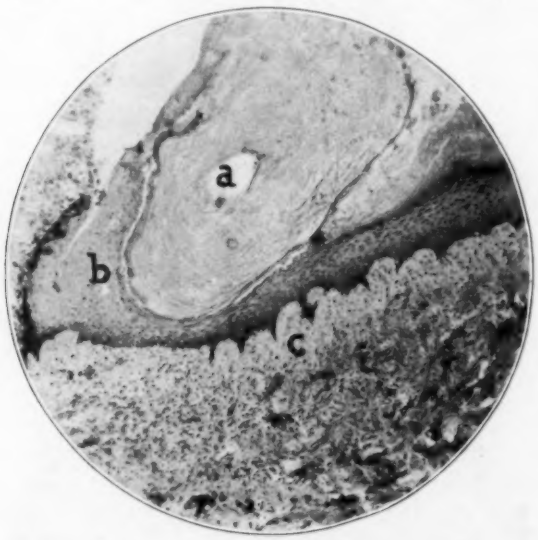

Fig. 15.—Section of a dermal implant at two months, showing the left angle of the epithelial cyst in figure 14 in detail; × 370. The cavity of the cyst, containing concentric layers of horny material, is indicated by *a;* the epithelium lining the cyst at the left angle, apparently turned to form the lining of the roof of the cyst, by *b,* and papillae beneath the epithelium of the floor of the cyst by *c.*

there was a series of concentric layers of pink-staining homogeneous material lying in a cavity which had no epithelial lining but was surrounded by granulation tissue above and the dense collagenous fibers of the implant below.

Sweat glands were present but were mostly poorly preserved, with the degenerative changes already described (fig. 19). There were several deeply placed collagenous fibers the same length as the implant (fig. 20).

The granulomatous response of the tissue at the site of implantation was marked. Between the skin and the implant there were two areas which showed a somewhat similar pattern—granulomatous nodules, rather large and oval, containing within their area many densely packed epithelioid cells with numerous

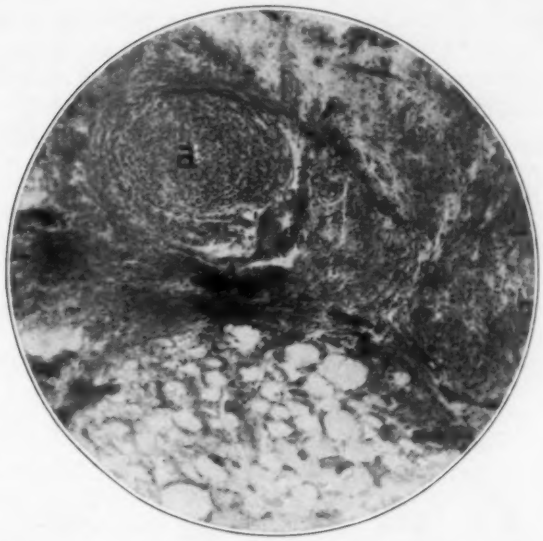

Fig. 16.—Section of a dermal implant at two months, showing a granulomatous nodule (*a*) with a fibrous capsule; × 100.

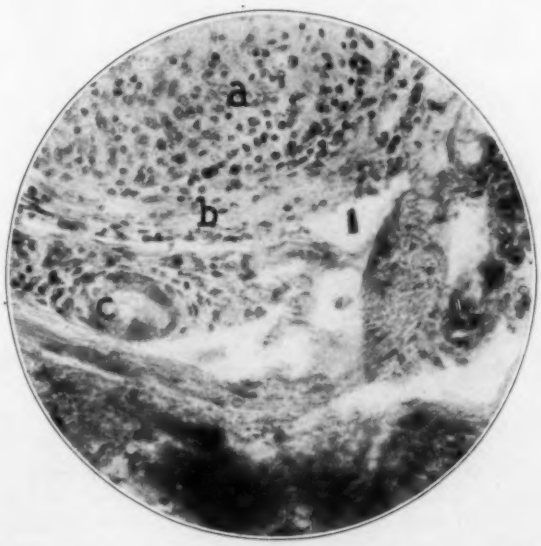

Fig. 17.—Section of a dermal implant at two months, showing in detail the same cyst pictured in figure 16; × 600. Cells constituting the granulomatous nodule are indicated by *a*, the capsule by *b* and a giant cell, adjacent to the area of the granuloma, by *c*.

giant cells. Within each of these areas of microscopic size were small angular refractive bodies, those in the area to the right being more definitely recognizable as hair sections and those in the area to the left, which were more angular, as perhaps remnants of hairs. The bodies in both areas were brownish.

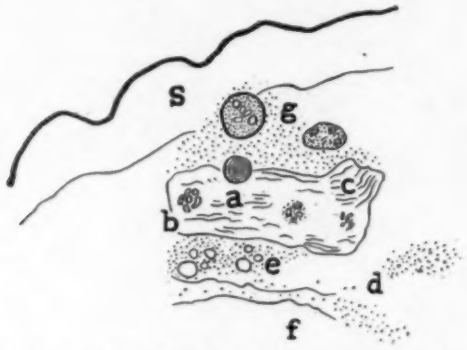

Fig. 18.—Diagram of a dermal implant at seven months. *S* indicates the overlying skin of the chest; *a*, a cyst containing horny material, without an epithelial lining; *b*, sweat gland tubules, showing partial degeneration; *c*, collagenous fibers of the implant; *d*, granulation tissue surrounding the implant; *e*, cavities in the granulation tissue surrounding the implant (granulomas?); *f*, deeply placed collagenous fibers of the implant, and *g*, granulomatous nodules.

Fig. 19.—Section of a dermal implant at seven months, showing partial degeneration of the sweat gland tubules; × 100. The sweat gland tubules, showing degenerative change, are indicated by *a* and the collagenous fibers of the implant by *b*.

Another feature of this section was the formation of large round cavities in the granulation tissue underlying the dermis. As they were surrounded by macro-

phages and epithelioid cells, they were believed to be similar in structure to the aforementioned granulomatous nodules, but with their contents lost in preparation.

The final section, obtained after one year's implantation, showed the implant in contact with the overlying skin along its whole upper border (fig. 21). Nevertheless, the probable upper margin of the implant could be recognized by comparing the depths of tissue in the region of the implant with that at both sides and by observing the newly formed layers of fibrous tissue. Along what appeared to have been the upper margin of the implant, there was a fairly large transversely elongate oval cavity, containing somewhat concentrically arranged horny material. There was no definite epithelial lining (fig. 22). The roof was formed by what was apparently a late or fibrous stage of granulation tissue, with a few small giant cells and some remnants of hairs. The floor was formed by the dense fibers

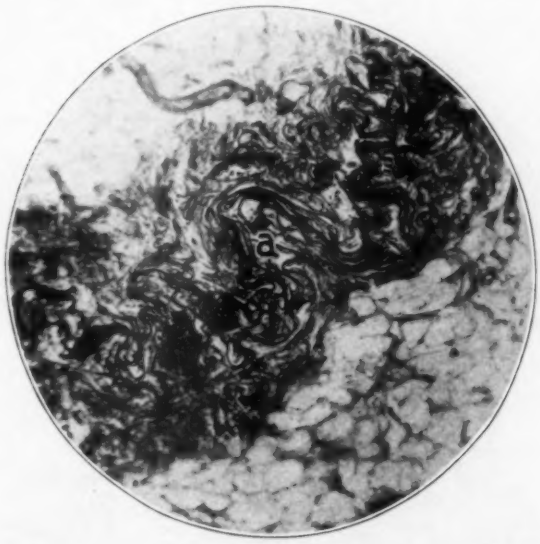

Fig. 20.—Section of a dermal implant at seven months, showing deep connective tissue fibers of the implant; × 100. The connective tissue fibers, showing waving and consqeuent longitudinal shrinkage of the implant, are indicated by *a*.

of the implant. No epidermal epithelium was seen in this implant. Sweat glands were present, but were altered in shape and showed degenerative changes in the epithelium of the tubules (fig. 23). No hair follicles were seen. In this, as in all the five preceding sections except the first, no sebaceous glands were found. The implant appeared rather densely adherent to the overlying skin, along its upper border. There was no definite evidence of granulation tissue except in the portion of the section overlying the implant in the region of the scar, where it was in a late stage. Beneath the implant there was rather normal adipose tissue.

COMMENT

From the sections described here it seems apparent that the epidermal tissue of the implanted dermal graft, although supposedly

removed, tends to survive.[16] Sebaceous glands were noted only in the section of the implant buried for one week, and hair follicles were found only in sections of the implants buried up to three weeks inclusive.

It may be claimed that epithelial tissue in these sections need not have been derived from the implant, since it was already present in

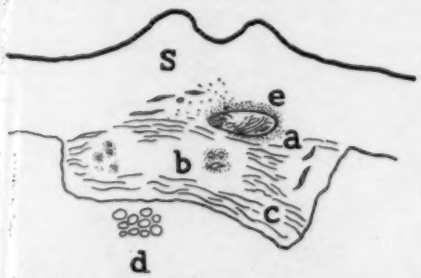

Fig. 21.—Diagram of a dermal implant at one year. *S* indicates the overlying skin of the chest, with which the implant has fused; *a*, a cyst, containing horny material and fragments of hairs; *b*, altered sweat gland tubules; *c*, collagenous fibers of the implant; *d*, fat; *e*, granulation tissue of the roof of the cyst, forming fibrous connective tissue.

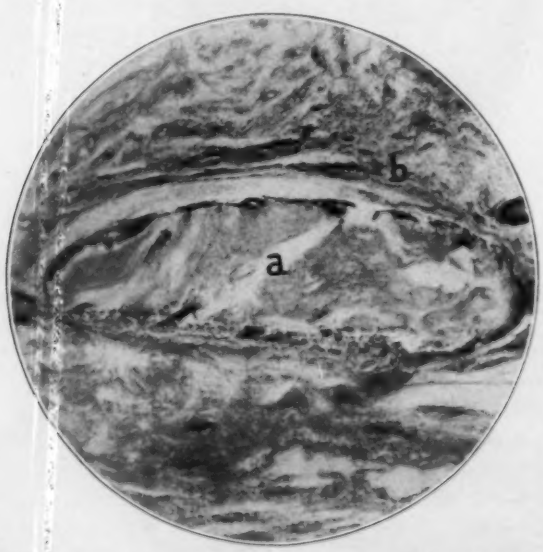

Fig. 22.—Section of a dermal implant at one year, showing a cyst without an epithelial lining; × 100. The cavity of the cyst, containing apparent horny material, is indicated by *a* and the wall of the cyst, showing absence of an epithelial lining, by *b*.

16. In one case of traumatic epithelial cyst of the hand, the original penetrating wound had occurred twelve years previously, and the secondary trauma one month previously (Wien and Caro).

the overlying skin at the time that the implantation occurred. Against this claim the following observation may be brought forward. The position of the epidermal remnant, whether in the form of an epithelial cleft, cyst, island [17] or fish-hook, was invariably found in the zone of the upper margin of the implant, which was exactly the former site of the epidermis of the implant (figs. 1, 6, 8, 13, and 21). The hair follicles were seen in their normal site in the implant (figs. 1 and 8), although many of the fragments of hairs had been displaced. The same normal position was true of the single sebaceous gland (fig. 1, *b*). These facts, in our opinion, should outweigh the more remote possibility that these structures had been displaced from the overlying skin. Since

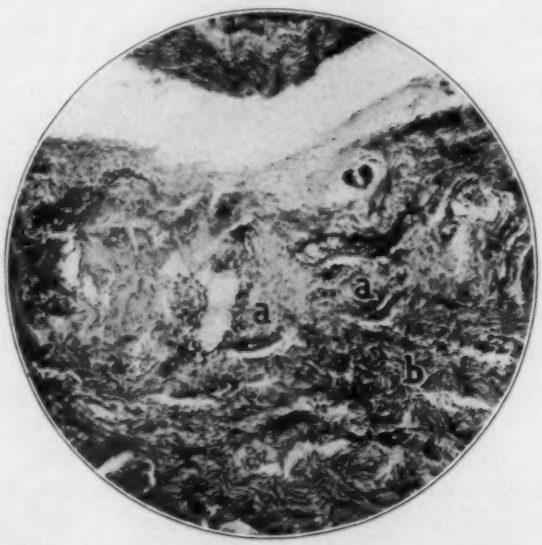

Fig. 23.—Section of a dermal implant at one year, showing persistent sweat gland tubules and degeneration; × 100. The sweat gland tubules are indicated by *a* and the collagenous fibers of the implant by *b*.

the cysts and other epithelial structures were all of microscopic size and of the same order of magnitude in the later as in the earlier sections, it is evident that they had not increased in size to any appreciable extent. In the case of an epithelial cyst of the palmar surface of the hand, which is traumatic in origin and subject to further trauma, it is noteworthy that such secondary trauma is mentioned as preceding the increase in size of the cyst to clinically appreciable dimensions. It may be that the site chosen for these implants is responsible for the lack of clinically demonstrable cysts. The site of the chest is

17. Zimches, in his implantation experiments with epithelium in dogs' muscles, at times obtained epithelial cysts and at other times solid islands of epithelium.

undoubtedly protected from trauma in comparison with the palmar surface of the hand. It is well to bear in mind the different functions of the skin due to the wear and tear of manual friction and the correspondingly greater thickness of the horny layer of the skin of the palmar surface.

However, in our experiments there was no evidence of deterioration of the buried epithelial remnants, with the possible exception of the two specimens of the longest duration, in which small cystlike cavities occurred without an epithelial lining (fig. 22). This evidence is speculative, since we do not know that these cavities were originally lined by epithelial tissue. At least the appearance of the earlier sections was normal as far as the epidermal cysts are concerned. The hair follicles, present only in the earlier sections (up to three weeks inclusive), appeared to be gradually developing into round epithelial cysts of microscopic size. The hairs, often displaced, were found in larger or smaller fragments both in the cavity of the cyst and scattered through the granulation tissue, especially in the centers of granulomatous nodules and within giant cells (fig. 24). Their demonstration was made easier by the use of polarized light, to which the displaced fragments, just as the normally placed intrafollicular hairs, gave a special rotation and diffraction (fig. 24). It is suggested that the granulomatous reaction is due, at least in part, to these structures which are especially resistant to solution and absorption.[18]

The changes in the sweat glands were much more marked in the later sections (figs. 19 and 23). It would seem that they were undergoing slow but continuous replacement by fibrous tissue. The lack of any sebaceous glands in all the sections except the first must be interpreted as a probable indication of their failure to survive, though this is not conclusive, as it is purely negative evidence based on a few specimens. Therefore, while some of the epithelial structures evidently tend to survive, our observations point toward their eventual disappearance.

It is evident that the fate of the true dermal structures as opposed to the epidermal structures is to survive by fusion with the subcutaneous tissue at the site of the implantation (fig. 21). This is mediated by the normal mechanism of inflammation and repair process, being evidently aseptic in all these sections, and the repair process being normal aseptic wound healing, complicated by the presence of foreign material (horny material and hair and lipoids) definitely productive of granulomatous tissue, which often reaches the extent of a heaping up of cells

18. Zimches gave a similar explanation.

of the macrophage type, epithelioid cells and even giant cells into diffuse tissue or nodules of microscopic size (fig. 16).

This extreme form of reaction is characteristic of the "foreign body" reaction and may occur in an epithelioma about the horny substance formed by excessive cornification of an epithelioma nodule (Muir [19]).

That this type of reaction is present in the sections obtained after seven months of implantation and almost absent in those obtained after one year of implantation probably means that this difficulty is at last surmounted and the unassimilable material successfully walled off at

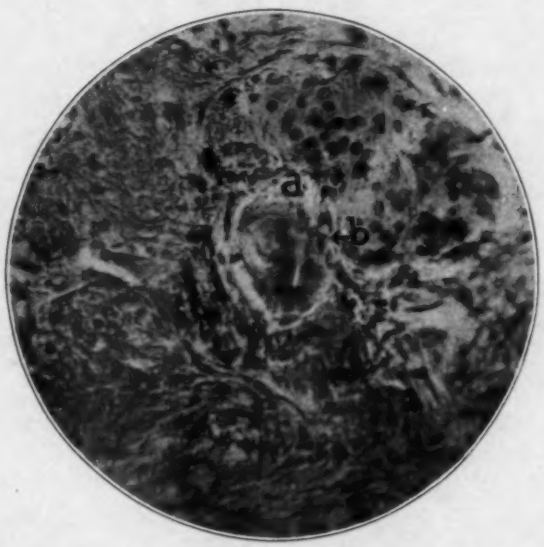

Fig. 24.—Section of a dermal implant, showing a foreign body giant cell in granulomatous tissue, and a foreign body derived from hair or horny material; × 600. The giant cell is indicated by *a* and the foreign body by *b* (foreign body demonstrated by use of polarized light).

the expense of increased fibrosis. It is possible, however, as has been suggested by Wien and Caro, that such a granuloma may lead to the formation of a cyst, the walls of the cyst containing granulation tissue with giant cells. They found one such cyst of clinically appreciable size in the hand after cutting by a sharp instrument. (The section is pictured in their article.) Such an explanation would require only the horny layer for the formation of a cyst. Our two final sections may represent microscopic cysts of this type.

19. Muir, Robert: Textbook of Pathology, Philadelphia, J. B Lippincott Company, 1924, p. 111.

CONCLUSIONS

The dermal graft (with epidermis apparently removed) when taken from the skin of the abdomen as a free auto-graft and inserted beneath the skin of the chest remained in place and fused with the surrounding connective tissue.

In the majority of sections, in spite of attempted complete removal of the epidermis, some epidermis remained. This remaining epidermis formed closed cyst cavities of microscopic size, containing horny material and fragments of hairs.

In the later sections (seven months and one year) horny material was seen in the cavities of microscopic size surrounded by granulation tissue without epithelial lining.

Sebaceous glands were noted only in the implants of one week's duration.

Hair follicles were observed only in the implants buried up to three weeks, inclusive.

Sweat glands were seen in all sections, but in later sections they were in the process of degeneration and fibrous replacement.

Granulation tissue surrounding the implant was of the chronic inflammatory type containing lymphocytes, macrophages, epithelioid cells and often giant cells, in some cases with the formation of granulomatous nodules.

In the granulomatous tissue surrounding the implant, at times within the implant, bodies were observed within the giant cells and nodules. These bodies resembled hairs and fragments of hairs.

REPAIR OF INDUCED BONE DEFECTS

CELLULAR CHANGES WHICH TAKE PLACE WITHIN THE FIRST FORTY-EIGHT HOURS

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Much excellent investigative work has been done in an attempt to determine the processes involved in the healing of bone injuries. Practically none of the reported data deal with those cellular changes which take place within the first forty-eight hours after the creation of the bone defect.

In this paper are given the results of experiments designed to determine the early cellular responses to trauma to the bone.

The plan followed in studying the processes of bone repair aims to evaluate the relative function and importance of the periosteum, cortex and marrow.

Investigation was confined to the repair of induced defects of the midportion of the diaphysis of a typical long bone, the tibia. The white rat was used as it is the laboratory animal which has been most frequently used by other investigators and hence concerning which there exist the most varied and exact data. The animals were raised and maintained on a diet adequate in caloric, mineral and vitamin content.

In order to control the influence, if any, of sex on the healing of bone defects, males and females were used in equal numbers. The age of the animal was considered of prime importance in determining the reparative response to trauma. In consequence, the various experiments were performed on a series of young animals and on an equal number of young mature animals.

The experiments were subdivided into three main groups:

1. Partial defect of tibial diaphysis (extending through the periosteum and the outer portion of the cortex)
   (*a*) Young animals
   (*b*) Mature animals

Aided by grant from the Faculty Research Committee.

Accepted as a thesis in qualifying for membership in the American Orthopaedic Association.

From the Laboratory of Orthopaedic Research and the Department of Pathology, University of Pennsylvania.

2. Hemisection of tibial diaphysis (extending through the periosteum, a portion of the cortex and into the medullary cavity)
   (*a*) Young animals
   (*b*) Mature animals
3. Complete section of tibial diaphysis
   (*a*) Young animals
   (*b*) Mature animals

(The data for groups 1*a*, 1*b* and 2*a* have been compiled and will be submitted for publication. Group 2*b* is considered in this paper.)

HEMISECTION OF THE MIDPORTION OF THE DIAPHYSIAL CORTEX (TIBIA) OF MATURE ANIMALS (2*b*)

MATERIAL AND TECHNIC

White rats of the Wistar Institute strain, of both sexes, varying from 190 to 260 Gm. in weight, were used. They were raised and maintained on a full maintenance diet.

After the induction of complete general anesthesia by the inhalation of ether, both hindlegs were thoroughly cleansed with 70 per cent alcohol.

Over either the crest or the anteromedial surface of each tibia, under aseptic precautions, a small linear incision was made through the skin and subcutaneous

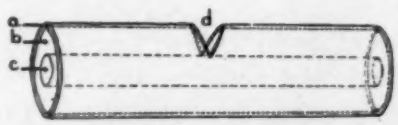

Fig. 1.—Diagram of the type of defect (hemisection) made in the tibial diaphysis: *a*, periosteum; *b*, cortex; *c*, medullary cavity, and *d*, defect.

tissues. Hemostasis was employed. The periosteum was exposed in an area devoid of large blood vessels, and a small, specially constructed osteotome was placed in contact with it. The osteotome was driven through the periosteum and the cortex into the medullary cavity by a blow from a small mallet. Care was taken not to induce complete fracture of the bone. The wounds were closed by interrupted sutures of fine silk. Both tibias of each animal were treated in the foregoing manner.

The animals were permitted to recover from the anesthetic and were then killed by inhalation of ether one, two, four, six, eight, twelve, sixteen, twenty, twenty-four, thirty, thirty-six, forty-two and forty-eight hours after operation.

Both lower legs of each animal were amputated at the knee, and from each the foot was removed at the ankle joint.

The legs were fixed in a dilute solution of formaldehyde U. S. P. (4 per cent) or in Müller's solution.

Pyroxylin sections of each tibia were made in accordance with the technic described in a former publication.[1]

1. Wagoner, George: The Technique of Preparing and Staining Large Bone Sections for Histological Study, J. Bone & Joint Surg. **13**:325-328, 1931.

Serial sections were cut through practically the entire defect of each tibia. The sections were stained with Hansen and Bock's iron hematoxylin.[2] The properties of the stain made it possible to study the bone in relation to the presence or absence of calcium. The sections were examined under the microscope with objectives of various powers, including the oil immersion.

HISTOLOGIC EXAMINATION

SERIES 501.—*Animal killed one hour after operation.*

A defect had been made in the midportion of the diaphysis of the tibia extending through the periosteum and cortex into the medullary cavity.

For a considerable distance on either side of the defect the periosteum was separated from the cortex, while the muscular fibers adherent to the periosteum were torn either completely or in part from their periosteal attachment. In the vicinity of the defect, the zone of uncalcified new bone lying immediately beneath the periosteum was stripped from the cortex so that the outer limit of the cortex was marked by the most recently formed cement line.

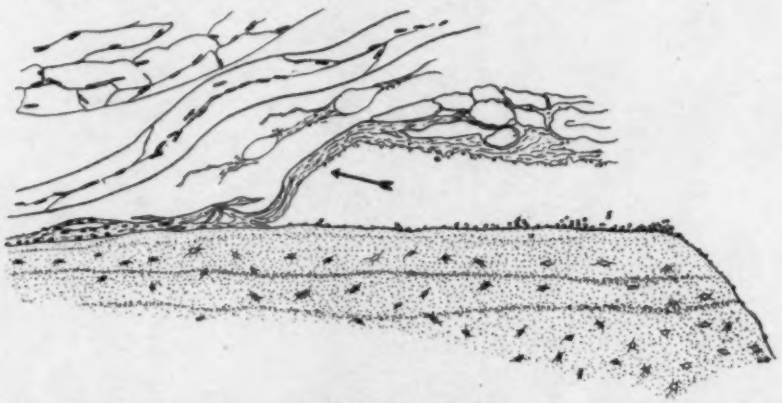

Fig. 2 (specimen 501).—Composite drawing made from study of numerous sections of a one hour defect, designed to illustrate stripping of the periosteum from the cortex in the neighborhood of the defect.

Immediately in front of and occupying the mouth of the defect were numerous muscle fibers. These were edematous and presented the typical appearance of cloudy swelling. Their cross-striations were absent through the greater portion of the tissue but remained present in a small portion of it. When present, the striations were vague and indistinct.

There was a small amount of fibrin in the outer portions of the defect and more particularly in its orifice.

Driven into the defect were many spicules of bone, occasional muscle fibers and at times a hair or two. Hemorrhage bound these structures together and completely filled the interstices of the defect. The amount of hemorrhage was not excessive and was only sufficient to fill the defect without piling the erythrocytes one on another. The muscle fibers present within the defect were not as edematous as those occupying the orifice. Their cross-striations were absent. The osteo-

2. The data contained in this paper were obtained from the study of approximately 2,500 stained and mounted sections cut from over 60 tibias.

cytes of the spicules of bone in the defect were occasionally degenerated and in some cases absent. In a number of other instances there was apparently no change in the osteocytes of these spicules.

The fibrillar (lamellar) structure of the cortical bone was beautifully illustrated by the occurrence of many bone "fibers," which closely resembled the strands or fibers of a rope. The cement substance which normally binds bone fibers together had given way before the impact of the osteotome, and the cut margins, instead of being sharply sheared, presented a frayed appearance.

It is of special note that the osteocytes of the outer cortical zone in the vicinity of the cut edges had undergone lysis. The lacunae were devoid of nuclei, and such cytoplasm as remained was faintly staining and of a granular texture.

Fig. 3 (specimen 501).—Photomicrograph showing fresh hemorrhage into the depths of the defect; × 250; one hour defect. Note the spicules of bone.

The canaliculi radiating from these lacunae stained more faintly than did those of the adjacent bone in which the osteocytes showed no evidence of solution.

There had been no extrusion of the cellular elements of the marrow into the apex of the defect.

SERIES 502.—*Animal killed two hours after operation.*

In this specimen the defect extended through the periosteum and cortex into the myeloid canal and by contrecoup through the opposite cortical wall. The subcutaneous tissues overlying the orifice of the defect were edematous and infiltrated with many polymorphonuclear leukocytes and large and small lymphocytes.

The double layer of osteoblasts lining the cortical margin was absent for a considerable distance on each side of the defect. The periosteal nuclei were absent in this same area. The fibers of the periosteum were distended by edema. The zone of uncalcified bone could not be seen.

The defect was filled with hemorrhage which was more dense than in section from the animal killed one hour after operation, and in it were found many lymphocytes and leukocytes. The hemorrhage had infiltrated the small spaces formed by the separation of the lamellae and thus extended into the substance of the cortex on each side of the defect throughout the entire depth of the cut. The lysis of the osteocytes had extended radially through a larger area than in the previous specimen. The cortical bone immediately adjacent to the defect stained more poorly than normally and was developing a granular character. The cut edges were less sharp and irregular. They seemed to be softer than the adjacent bone.

The cellular elements of the medullary cavity had extruded into the apex of the defect and were displacing the hemorrhagic elements. The marrow cavity itself was almost entirely devoid of hemorrhage, and no change could be detected in the composition or in the arrangement of the cellular elements of the marrow in the vicinity of the cut.

SERIES 504.—*Animal killed four hours after operation.*

The soft tissues, chiefly muscle, overlying the cortex of the bone at the site of the defect were edematous, but to a lesser degree than in the earlier specimens. The fibers and bundles were more closely packed, whereas the areolar tissue between them was less prominent. There was a distinct numerical decrease of infiltrating leukocytes and lymphocytes.

The periosteum in the vicinity of the defect was in closer approximation with the cortex of the bone, and in places was in direct contact with it. The periosteal layer of osteoblasts had approached the mouth of the defect, and there was a resumption of the proliferation of new osseous tissue.

The fibrinous network occupying the orifice of the defect was more dense and was undergoing organization. Particles of muscle previously present had undergone almost complete degeneration. The spicules of bone had lost their cellular character and were in the process of decalcification. Cellular resorption of these spicules was not present. Osteoclasts could not be seen in or near the defect.

There was almost complete disappearance of the erythrocytes, formerly seen in such profusion in the defect. The marrow elements had extruded higher into the defect and were practically replacing the hemorrhage. The interstices in the lower half of the defect were filled in by the marrow elements.

The zone of osteocytic degeneration in the adjacent cortex had increased.

The edges of the cut cortex showed still further absorption and rounding off of their formerly sharp and irregular margins, and for a small distance into the cortex the bone in this area had lost its staining properties to a great degree. A pale pink-staining slightly granular material was invading the defect from the upper surface of the cut edges of the cortical bone. Occasional cells, both polymorphonuclear leukocytes and monocytes, were scattered throughout this pink-staining material.

Those spicules of bone which had been pushed into the marrow cavity were rapidly losing their cellular structure through the death of the contained osteocytes and the obliteration of the canaliculi and cement lines. The spaces between the bone fibers had increased, and the intrusion of the myeloid elements into these spaces had increased. The spicules in the defect had lost to a marked degree the property of absorbing the hematoxylin stain. A definite granularity appeared

throughout the spicules; their margins, losing their sharp, well defined surface, were becoming softly irregular. At one or two points the lodgment of osteoclasts, with resultant lacunar absorption, could be detected. The almost complete absence of osteoclasts with their resorptive lacunae was conspicuous.

With the exception of a slight amount of hemorrhage in the marrow substance in the immediate vicinity of the depressed bone fragments, the cellular marrow presented no apparent abnormalities.

SERIES 512.—*Animal killed twelve hours after operation.*

The edema of the muscle tissues adjacent to the defect was markedly diminished, and, for the most part, the bundles had returned to normal size but continued to be deficient in nuclei. Some of the bundles were undergoing degeneration and absorption (lysis).

Fig. 4 (specimen 512).—Photomicrograph showing progressive resorption of spicules of bone and filling of lamellar interspaces with marrow elements and an absence of osteocytes. Hansen and Bock's iron hematoxylin stain; × 180; twelve hour defect.

The defect was solidly filled with bone chips, cellular elements of the myeloid canal and blood; all were bound together in a strong, well organized mass of interlacing fibrous strands. The hemorrhage was beginning to disappear.

Those bone chips lying in the subcutaneous tissues outside of the defect stained poorly, had lost for the most part their cellular detail and were in the process of absorption (necrosis). Osteoclastic resorption of these fragments was absent.

The presence of marrow elements in the defect and in the spaces created between the bone fibers was more marked than in previous specimens. Evidence of hemorrhage in the deeper portions of the defect was conspicuously lacking. The bone chips lying within the defect had undergone more degeneration than those in the subcutaneous tissues. There did not seem to be an extension of the zone of osteocytic degeneration except perhaps to the area in the external cortical zone immediately beneath the periosteum. The general appearance was that of a fairly firm mass of heterogeneous tissues filling the defect in all parts and bound together and to the adjacent bone by proliferating strands of fibrous tissue.

Fig. 5 (specimen 530).—Photomicrograph showing a transverse fracture and longitudinal separation of the cortical lamellae; filling of the interspace, and death and lysis of osteocytes. Hansen and Bock's iron hematoxylin stain; × 245; thirty hour defect.

Monocytes and numerous macrophages were in contact with the bony walls of the defect. Lacunar resorption was present. No osteoclasts were found in the lacunae, the cells therein being chiefly macrophages. Many phagocytosed red blood cells were present in this area.

Within the focal areas of necrosis of cortical bone, adjacent to the myeloid cavity, there was marked invasion of the necrotic tissue by neutrophils.

The monocyte resistance was as yet not great.

No hemosiderin crystals were noted.

The cells found in the outer portion of the defect were those which would arise from blood vessels, namely, nonnucleated red cells, old polymorphonuclears, leukocytes and small round lymphocytes. The majority of these cells were undergoing degeneration.

SERIES 516.—*Animal killed sixteen hours after operation.*

This specimen was distinguished by the greater density of the material filling the defect and by the greater distance with which certain of the cellular elements of the marrow had emerged into the defect. Under oil immersion it was possible to see lacunar resorption in the depths of the defect and in the isolated spicules of bone. The cells engaged in the resorption of bone were not osteoclasts but wandering macrophages derived from the reticulocytes.

Fig. 6 (specimen 530).—Photomicrograph showing fractured and separated lamellae; an absence of osteocytes, and interspaces packed with cellular myeloid elements. The arrow indicates the giant macrophage. Hansen and Bock's iron hematoxylin stain; × 846; thirty hour defect.

Hemorrhage of the marrow was absent. To one side of the defect and along the endosteal margin was a narrow band of edema. (This may have been an artefact, as in places the endosteal layer of osteoblasts was detached from the surface of the bone.) Edema certainly was present in adjacent areas.

It is of interest that the cells of the bone marrow lying in the defect and those in the canal immediately below the defect had a vertical arrangement—at right angles to the long axis of the bone. This was in contrast with the distant areas of the medulla where the hematopoietic cells had no definite arrangement.

SERIES 520.—*Animal killed twenty hours after operation.*

There was a moderate degree of extra-osseous inflammatory reaction. The cells present were fixed tissue cells and wandering macrophages. Some fibrin was still present. A small amount of necrotic tissue remained, but the work of the scavengers had been well done.

The periosteum was detached in the vicinity of the defect. The orifice of the defect contained a loose skein of fibrin in which were enmeshed numerous migratory cells which may have come either from the blood or from the myeloid cavity. Many of these cells were neutrophils, while an almost equal number were macrophages. Deeper in the defect the fibrin was more dense, but it became less dense as the apex was approached. Necrotic muscle strands and spicules of bone were present. Disintegrating erythrocytes were present in small numbers. At the apex of the defect hematopoietic tissue formed the main contents together with a small amount of fibrin and a few erythrocytes. Similar contents filled the clefts between the frayed cortical lamellae.

Lacunar resorption was not as apparent in this specimen as in the two earlier ones.

The medullary contents were normal; neither hemorrhage nor deposits of hemosiderin were noted.

SERIES 524.—*Animal killed twenty-four hours after operation.*

The orifice of the defect was completely bridged over by the extra-osseous tissue. The outermost layer was comprised of muscle bundles, which were edematous. The bundles were separated, and in the interstices deposits of fibrin were present. In the meshes of the fibrin network were many wandering cells, chiefly lymphocytes and polymorphonuclear leukocytes. Some of the muscle fibers were fragmented, and the fragments were necrotic. As the mouth of the defect was approached, the deposit of fibrin became more dense. It had completely replaced the areolar tissue. It was arranged in dense whorls and heavy strands throughout which were many wandering cells. No bacteria were seen. Few erythrocytes were present.

The periosteum, the subperiosteal osteoblasts and the layer of uncalcified bone were present on each side of the defect up to the margins of the cleft. These gave the appearance of having been detached but reunited to the cortical bone.

The material filling the defect was in contact with its sloping sides to which it was firmly united. The cortical margins of the defect were granular and poorly staining and showed marked erosion and softening.

The osteocytes in the vicinity of the defect were for the most part absent, and their lacunae were filled with faintly-staining granular material; the canaliculi were indistinct.

The spicules of bone in the defect were in various stages of lysis, those at the bottom being more necrotic than those elsewhere.

Myeloid elements occupied the lower third of the defect. Practically no hemorrhage was present in the defect, and no hemosiderin crystals could be seen.

In the spaces formed by the fraying of the cortical lamellae, erythrocytes and myeloid macrophages were found. The adjacent bone tissue was markedly necrotic. Lacunar resorption by the macrophages was present but not in sufficient degree to account for the amount of bone necrosis which was present in and about the defect.

The contents of the myeloid cavity presented no abnormality except for a possible condensation of the cellular elements immediately below the apex of the defect.

SERIES 530.—*Animal killed thirty hours after operation.*

The orifice of the defect was completely closed, and over it the periosteum had reformed. There were, however, no layers of osteoblasts in the immediate vicinity of the defect.

The contents of the defect were less cellular than those of the previous specimens. The fibrin was compact and beginning to undergo organization. There was some fibroblastic proliferation within the marrow tissue of the defect.

Within the medullary cavity immediately below the end of the cortical defect there were grouped along the opposite cortical wall and for a short distance into the cavity a large number of marrow giant cells, megakaryocytes and macrophages. As the apex of the defect was approached it was seen that the major portion of

Fig. 7 (specimen 530).—Photomicrograph illustrating the breaking of the cortex into strands and the zones of osteocytic degeneration. The upward extension of the marrow elements into the defect is shown together with the organization of the contents at the orifice of the defect. Hansen and Bock's iron hematoxylin stain; × 100; thirty hour defect.

the material extending downward from the defect was without structure and that it consisted almost entirely of cellular débris and irregular granular masses which were in the process of fusion. Scattered in clumps throughout this material were numerous giant cells and other scavengers. Extending further upward into the defect the material filling it was more acellular and structureless than that in the vicinity of the medullary cavity. The upper third of the defect, however, was filled with newly extravasated red blood cells, together with occasional polymorphonuclear leukocytes and lymphocytes.

As the interstices between the bone fibers were examined, it was found that their contents closely resembled the contents of the defect in its lowermost portion, except for the fact that degeneration of the cellular contents had not proceeded so far. It was possible to identify the various phagocytic marrow cells lying therein. They were surrounded by products of their digestion. One or two of the interspaces had been filled by red blood cells and gave the appearance of recent secondary hemorrhage. In several of the interspaces evidence of fairly recent vascular hemorrhage was present, and among the clumps of red cells were to be found marrow giant cells busily digesting them. The material filling the defect was in close and intimate approximation to the cortical walls. Large lacuna-

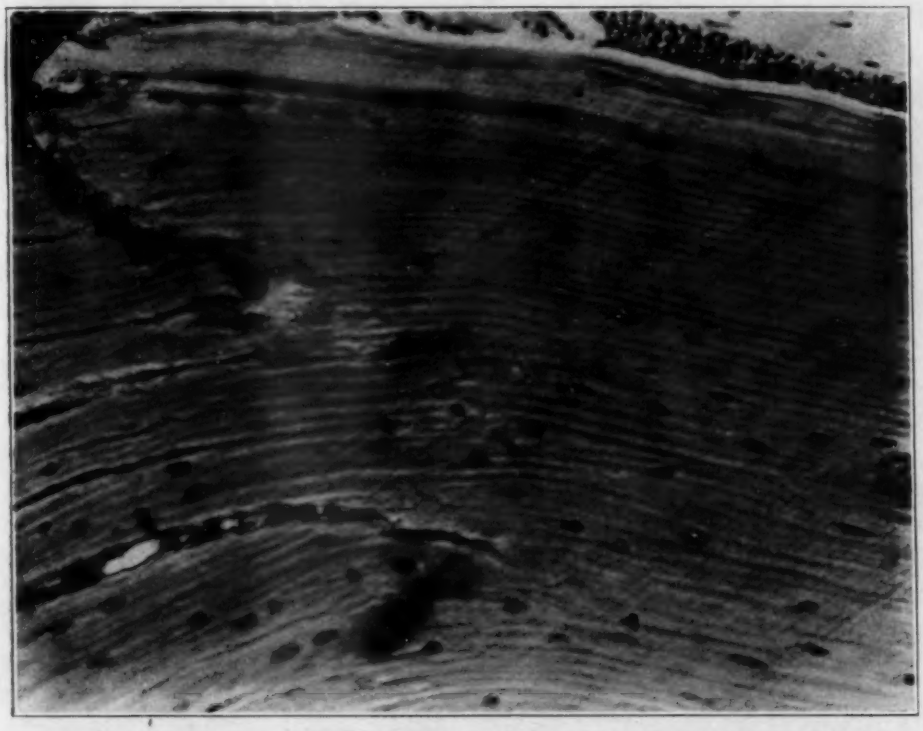

Fig. 8 (specimen 530).—Photomicrograph showing the cortical zone adjacent to the defect. Note the piling up of osteoblasts at the outer margin and their approach to the defect; the fibrination of the cortex with separation between the longitudinal lamellae and the filling of the created interspaces with cellular elements, and particularly the absence of all osteocytes, excepting five in the lower right corner. Hansen and Bock's iron hematoxylin stain; × 315; thirty hour defect.

like bays were found along the margin of the walls, and in a number of these could be seen the remnants of huge phagocytic cells. Nowhere was it seen that the cortical walls of the defect were possessed of sharp edges. These had all been smoothed and rounded off, and there had extended peripherally from the defect a marked degree of decalcification of the adjacent bone.

Such bone varied from a homogeneous, structureless mass to one in which canaliculi and some lamella could be seen. The Howship lacunae in this area, however, were devoid of osteocytes. Their peripheral wall was faintly staining, as were the canaliculi radiating from them.

SERIES 536.—*Animal killed thirty-six hours after operation.*

The defect was overlaid with a mass of extra-osseous tissue, chiefly muscle, the individual fibers of which were somewhat edematous and were separated from one another. Those fibers which had been traumatically fragmented had undergone practically complete necrosis. There was a marked infiltration of neutrophils. These cells occupied the spaces between the muscle fibers and were lodged in the

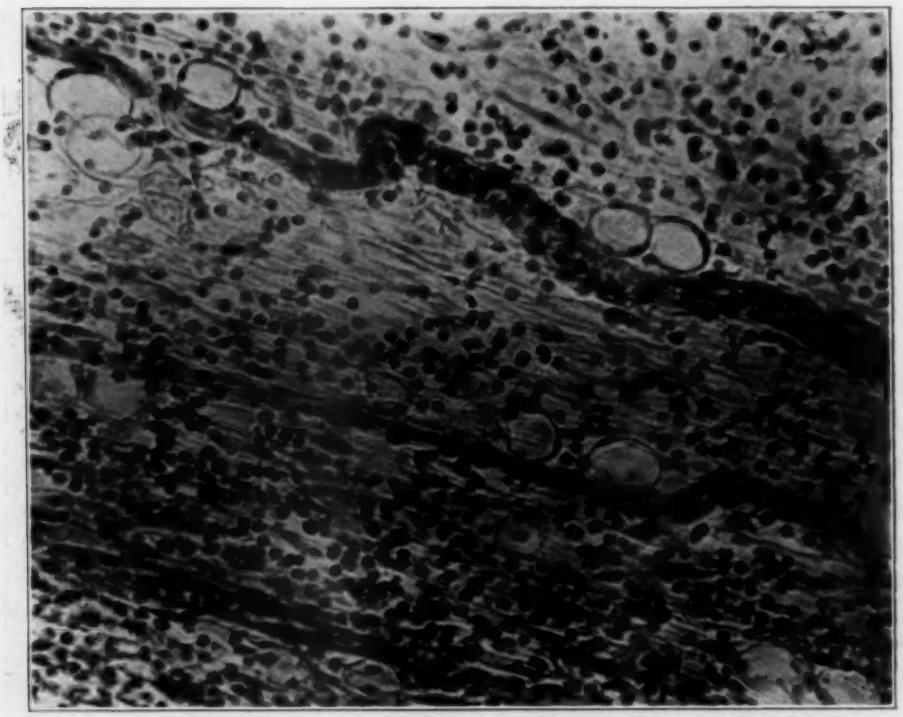

Fig. 9 (specimen 542).—Photomicrograph showing newly formed capillaries in the extra-osseous tissue growing toward the orifice of the defect. Hansen and Bock's iron hematoxylin stain; × 277; forty-two hour defect.

thick network of fibrous tissue, which was rapidly undergoing organization. Scattered throughout the extra-osseous tissues were many spicules of bone of varying size; the smaller ones had undergone almost complete necrosis. The larger ones presented varying degrees of destruction. Although both large and small spicules showed the frequent occurrence of lacunar resorption by macrophages, the number of these cells so engaged seemed too few to be responsible for the amount of resorption presented by the fragments of bone. One obtained the impression that the major portion of the bone lysis was the result of chemical activity rather than of cellular resorption. Very few red cells or their remnants could be seen throughout the extra-osseous tissue. Several depositions of hemosiderin were present.

The periosteum had been loosened from its cortical attachment for some distance on each side of the defect, and the space thus created was filled by a dense fibrous network in which were lodged numerous wandering cells in varying stages of destruction. There was a reappearance of the layer of subperiosteal osteoblasts. These cells were actively engaged in the formation of new bone and were extending toward the margins of the defect. Throughout the cortex beneath the disturbed periosteum and for a considerable distance on each side of the defect there had been destruction of practically all the osteocytes.

The cortical margins of the defect showed more active resorption by macrophages than had been noted in any of the other section specimens studied.

Fig. 10 (specimen 542).—Photomicrograph showing a central marrow capillary bending outward to the base (apex) of the defect. Note the radial alinement of the marrow elements. Hansen and Bock's iron hematoxylin stain; × 92; forty-two hour defect.

Although there had been separation of the lamellae of bone along the cement lines, the fimbriation of the cut edges was less marked than previously. There was active invasion of the artificial interspaces between the lamellae by the marrow cells. The lower third of the defect was filled with myeloid cellular material, while the upper two thirds was filled with a dense mass of fibrous tissue undergoing organization, partly resorbed spicules of bone and a rather numerous infiltration of wandering myeloid and blood cells.

SERIES 542.—*Animal killed forty-two hours after operation.*

Throughout the extra-osseous tissue there was a distinct subsidance of the inflammatory reaction and the begining of definite organization. A marked

ingrowth of new capillaries was present. These new capillaries extended to the margins of the defect but had as yet not invaded the material filling the defect.

The subperiosteal osteoblastic zone showed definite proliferation on each side of the defect and was in close proximity to its margins. The continuity of the periosteum was being restored. The degeneration of the fragmented muscle fibers and of the small spicules of bone lying in the extra-osseous tissues was well advanced, being almost complete for the muscle and partially so in the case of the bone. The orifice of the defect was solidly capped by well organized fibrous tissue in the meshes of which the number of neutrophils had decreased. Practically no red blood cells were now visible in the material

Fig. 11 (specimen 542).—Higher power magnification of the central marrow capillary illustrated in figure 10. Hansen and Bock's iron hematoxylin stain; × 277; forty-two hour defect.

occluding the outer portion of the defect. Occasional deposits of hemosiderin crystals were present in this outer zone. The midportion of the defect contained the remnants of erythrocytes, among which were intermingled the protruding elements of the myeloid canal. The deeper portion of the defect was completely filled with myeloid elements. These also penetrated latterly into the interstices formed by the separation of the lamella. The spicules of bone lying in the defect were rapidly undergoing resorption, and considerable lacunar resorption was being carried out along the margins of the spicules and lamella by the myeloid macrophages. Extending outward from the bottom of the defect were many strands of fibrous tissue, between which were found the granulocytic

cells of the marrow cavity. The zone of osteocytic degeneration, both in the cortex along the margins of the defect and beneath the elevated periosteum, had apparently not increased in size. But it was now quite difficult to recognize the lacunae in which these cells formerly lay, and the canaliculi could not be distinguished.

In the central portion of the myeloid canal in several of the sections was seen a large arteriole running parallel to the long axis of the bone. At the point below the apex of the defect this arteriole was bent in a sharp curve (hairpin curve) toward the apex of the defect. In this same area a radial alinement of the marrow cells was quite apparent. These radiating cell lines had for their center a point in the lower portion of the defect. In several of the

Fig. 12 (specimen 542).—Photomicrograph showing myeloid elements extending into the defect. A capillary is present in the defect. Note also the fraying of the cortex and absence of osteocytes. Hansen and Bock's iron hematoxylin; × 240; forty-two hour defect.

sections there was a small arteriole extending upward in the central portion of the defect for approximately two thirds of its depth. The vessel was probably an offshoot of the large central marrow arteriole arising from the apex of its curve.

SERIES 548.—*Animal killed forty-eight hours after operation.*

The orifice was completely closed by overlying muscle and areolar tissue. The muscle fibers were not edematous. The cellular infiltration noted in the previous specimens was present in a lesser degree. There was, however, a vast

invasion of actively proliferating fibroblasts and the formation of numerous capillaries. The capillaries had reached the orifice of the defect and were bending downward to penetrate the material occluding it. The periosteum had become reattached to the cortical bone, and at points distant from the defect the osteoblastic layer had reformed and was actively engaged in the formation of new uncalcified bone. It was easily demonstrable that that portion of the periosteum in which reestablishment of osteoblastic activity had taken place was recently separated from the cortex of bone. This was proved by the condition of the extra-osseous tissues, which showed infiltration of cells, the presence of

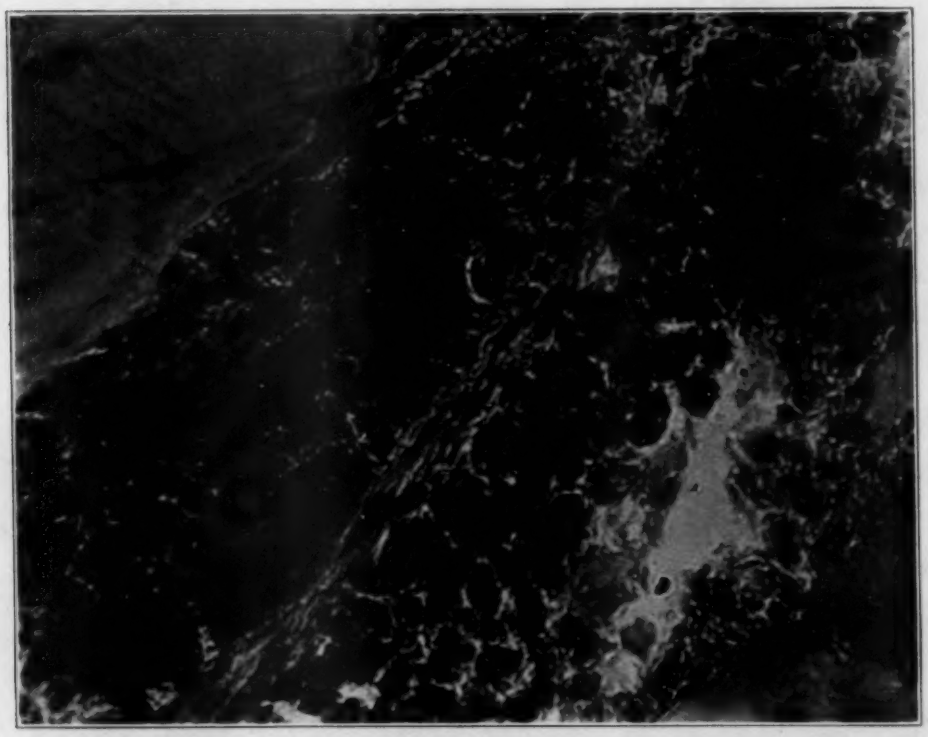

Fig. 13 (specimen 542).—Photomicrograph showing a small capillary from the marrow cavity extending upward into the defect. Note in addition the myeloid elements in the defect and the absence of osteocytes in the lacunae. Hansen and Bock's iron hematoxylin stain; × 690; forty-two hour defect.

granulation tissue and a disturbance of muscle fibers. Furthermore, immediately beneath the portion of the periosteum under discussion the osteocytes lying in the cortex were dead. It was possible, therefore, to state definitely that periosteal reattachment had occurred and that with the reattachment there had been resumption of osteoblastic activity.

The entire defect was solidly filled with dense fibrous tissue undergoing organization. The presence of small islands of pink-staining homogeneous material marked the sites formerly occupied by spicules of bone. In the outer half of the defect it was impossible to note cellular detail, the infiltrating cells having

undergone necrosis. Occasionally in the lower half of the defect isolated giant macrophages could be recognized. The edges of the cortical margins of the defect were frayed and appeared soft and mushy. Some osteoclastic resorption was present but to a lesser degree than in the previous specimens.

SUMMARY

A definite sequence of events followed the making of a defect (hemisection) in the tibial diaphysis of living white rats.

The periosteum was detached from the cortex for some distance on each side of the defect. With this detachment of the periosteum the underlying layer of osteoblasts was destroyed. The zone of newly formed but uncalcified bone in this area was obliterated. Such complete derangement of these structures resulted in interference with the periosteal blood supply to the underlying cortex of bone. In consequence, nutrition of the cortical bone in this area was impaired. Such nutritional impairment was evidenced by necrosis and lysis of the osteocytes. The area of cortical bone so involved increased from hour to hour until the maximum area deriving its nutrition from vessels passing through the deranged periosteal zone was involved. In like manner, the nutrition of the cortex adjacent to the defect was impaired, and its osteocytes were destroyed.

The second interesting fact was the manner in which the cortical bone responded to the trauma incident to the creation of the defect. In adult rats one would expect the cortex to be cut sharply by the osteotome. Instead, it responded in a manner which clearly characterized its structure and physical properties. The cut edges of the defect instead of being sharp showed marked fraying. The fraying corresponded to the longitudinal lamellae of the bone. These lamellae became separated one from the other along their long axes. Separation took place at the cement lines which normally bind the lamellae together. (When bound there is no indication of these lines of weakness.) Furthermore, the intrinsic malleability of the cortical bone was manifested by the manner in which these separated lamellae bent inward before the force of the blow. In some cases this bending equaled an angle of 90 degrees.

Of course, small spicules of bone were broken off and forced into either the extra-osseous tissues or into the defect.

Similarly, fragments of soft tissue, chiefly muscle, were also created. These fragments of muscle, together with the traumatized muscle fibers in the vicinity of the wound, showed marked edema and cloudy swelling at the end of one hour.

The defect was at first filled with erythrocytes as a result of hemorrhage from the several small extra-osseous vessels. Occasional bands of fibrin formed within the first hour. By the second hour there was

present in the extra-osseous tissues and at the mouth of the defect a general invasion of neutrophils. The local edema of the tissues was increased, and marked lysis of the damaged muscle fibers and fragments was well advanced. The hemorrhage within the defect was increased, and the spaces between the separated lamellae were filled with hemorrhagic elements. The zone of osteocytic death had extended by the end of the second hour, not only in that area beneath the stripped periosteum but on each side of the defect. The cut edges of the bone were less sharp, and there was a beginning granularity of the cut margins.

No change could be noted within the myeloid canal.

The third interesting and perhaps most important phase of repair was evidenced by the appearance of myeloid elements within the defect. These elements were first noted in the bone section obtained two hours after operation. They appeared first at the apex of the defect but gradually extended higher into the defect, replacing the hemorrhagic elements which first occupied the breach. It is difficult to determine the manner whereby the myeloid elements entered the defect. Certainly the major portion of the cellular elements found in the defect were those of the migratory type. One cannot say if actual migration, the result of chemotaxis, was the responsible agent. Variation in pressure between the marrow cavity and the osseous defect doubtless existed, and it seems probable that a greater positive pressure, the result of its vascular plexus, existed in the marrow cavity than in the avascular defect. Such difference of pressure would account for the gradual extrusion of the myeloid elements into the defect. The trauma incident to the creation of the defect cannot be responsible for the presence of marrow elements in the defect for two reasons: First, the marrow elements were not present in the earliest sections (one hour after operation), and, second, the lines of force of the trauma would be such as to force the marrow contents away from rather than into the defect.

It is of extreme interest that through practically the entire series of sections osteoclastic resorption of bone was absent. Only occasionally was there found in the large number of sections examined an osteoclast lying within a lacuna of resorption. In the later sections (from the twelfth hour on) cellular resorption of bone was occasionally encountered. The cells so engaged were not true osteoclasts but were giant macrophages arising from the reticulo-endothelial system of the myeloid cavity. Despite the absence of cellular resorption there was marked evidence of bone resolution, as indicated by the progressive rounding off of the edges of cortical bone, by the granularity of the bone along the margins of the defect and by the removal of calcium from the cortical bone, as indicated by its poorer staining properties.

In addition, the spicules of bone lying both within the defect and within the extra-osseous tissue showed progressive evidence of solution. One is forced to the expression of opinion that such bone solution as was most definitely occurring must have been taking place through the process of chemical activity rather than through the medium of individual cell action.

As the age of the defect increased the organization of the material filling the defect proceeded. Its cellular structure became obliterated, and the whole gradually changed into an acellular mass of material firmly bound together and to the walls of the defect by dense strands of fibrous tissue. The periosteum gradually became reattached to the periphery of the cortex; hyperplasia of the osteoblastic layer and the reformation of a new zone of uncalcified bone were progressive changes. In the later sections these peripheral changes were seen to approach the margins of the defect.

In the sections obtained forty-two hours after operation newly formed capillaries were seen in the extra-osseous tissue rapidly growing toward the margins of the defect. In the sections obtained forty-eight hours after operation the capillaries had reached the orifice of the defect and were beginning to turn downward to penetrate the fibrous mass filling the defect. At the same time there was evidence of beginning capillary penetration from the myeloid cavity.

In this paper are described the salient progressive changes which take place within the first forty-eight hours after the creation of a defect in the midportion of the diaphysis of the tibia of the rat, the defect extending through periosteum and cortex into the marrow cavity. The changes were constant, definite and characteristic. No influence of sex on the rate or character of the reparative processes was noted.

CERVICAL RIB ASSOCIATED WITH ANEURYSM OF THE SUBCLAVIAN ARTERY

REPORT OF A CASE AND REVIEW OF THE RECENT LITERATURE

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The occasional presence of cervical ribs in human skeletons was known to Galen, but the first description of a case must be ascribed to Hunauld in 1742. Operative resection of a cervical rib was first carried out by Coote in 1861. Between 1861 and 1895 only eight cases were reported in which operation was performed. Since that time each year has brought increasing numbers of case reports and successful operative results, so that at present cervical rib can hardly be considered a clinical rarity. Of the recognized complications, however, aneurysmal dilatation of the third portion of the subclavian artery is rare. In 1907 Deitmar [1] attempted to collate the literature on this subject and collected reports of five cases, one a doubtful one. Streisler's [2] monograph on cervical rib in 1913 did not add reports of any new cases despite a complete review of the literature. In 1916 Halsted [3] reviewed the reports of seven hundred and sixteen cases of cervical rib, including the available total of clinical, autopsy, and museum material. He reported that aneurysm of the subclavian artery or some degree of dilatation in that vessel was noted in twenty-seven instances. Adson,[4] whose wealth of experience in the operative treatment of this condition has been unique, stated in 1933 that he had never encountered an example of subclavian aneurysm in association with cervical rib.

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1. Deitmar, cited by Halsted.[3]

2. Streisler, E.: Die Halsrippen, Ergebn. d. Chir. u. Orthop. **5**:280, 1913.

3. Halsted, W. S.: An Experimental Study of Circumscribed Dilatation of an Artery Immediately Distal to a Partially Occluding Band, and Its Bearing on the Dilatation of the Subclavian Artery Observed in Certain Cases of Cervical Rib, J. Exper. Med. **24**:271, 1916.

4. Adson, A. W.: Surgical Treatment of Cervical Ribs, Texas State J. Med. **28**:739, 1933.

It is the purpose of the present communication to record a new case of subclavian aneurysm in association with cervical rib and to correlate it with cases reported in the literature since Halsted's summary in 1916. There are three of these cases, in two of which the diagnosis was verified by operation.

In May 1922 Moore [5] reported a case, that of a painter aged 55 whose chief complaint was cough. An incidental and symptomless finding on physical examination was an expansile pulsatile swelling, the size of a walnut, in the left supraclavicular region. Neither thrill nor bruit was present. There was no palpable difference in the radial pulses. Just behind and medial to the pulsatile swelling, a bony protuberance could easily be felt. A roentgenogram showed a cervical rib bilaterally, the right with a free end and the left fused to the first thoracic rib. The Wassermann reaction of the blood was reported as strongly positive. At operation an aneurysm was found in the third portion of the subclavian artery. It appeared as a saccular diverticulum the size of a cherry and sprang from the anterior wall of the vessel. The subclavian artery was otherwise normal. The rib was excised and showed a definite neurovascular groove. The aneurysm was doubly ligated in situ without removal. The radial pulse began to reappear on the fourth day.

In October 1931 Billington [6] described the case of a 42 year old woman who had suffered from pain in the back and in the left shoulder for several years. In May 1930 her physician discovered a tumor above the left clavicle. She began to have pain in the left arm. A difference was noted in the timing of the radial pulses. In June the radial pulse on the left had disappeared, and the arm felt cold. When the patient was admitted to a hospital in November 1930, the fingers of her left hand were cold, numb and pale. A nonpulsatile swelling 2½ inches (6.3 cm.) in length and about the diameter of a walnut was observed above the left clavicle. The left radial pulse was not palpable; there was no motor weakness. The Wassermann reaction of the blood was reported to be negative. A roentgenogram showed a completely developed cervical rib on the right and an incomplete one on the left fused to the first thoracic rib. At operation, through a 4 inch (10 cm.) supraclavicular incision, an aneurysm of the subclavian vessel was exposed. It was adherent to the lower cord of the brachial plexus and was removed by double ligation and section. The cervical rib

5. Moore, C. A.: A Case of Subclavian Aneurysm with Cervical Ribs, Lancet **1**:1045, 1922.

6. Billington, W.: Excision of Subclavian Aneurysm Associated with Cervical Rib, Brit. J. Surg. **19**:334, 1931.

associated with this aneurysm was not removed since it did not seem to impinge on the lower cord of the brachial plexus. The excised aneurysmal specimen was found to measure 2½ inches (6.3 cm.) in length and ¾ inch (1.9 cm.) in width. The sac was filled with a laminated thrombus showing a minute central channel. There was no microscopic evidence of primary disease in the intima. The muscularis showed some fibrosis, and the internal elastic lamina was duplicated in places and fragmented. The patient made a good postoperative recovery and was completely relieved from pain.

Quinn and Davison [7] in 1934 described the case of a widow of 75 years who had first noticed a pulsatile swelling on the left side of the neck thirty years previously. One month prior to her observation by the authors she fell on her left shoulder and for the first time began to experience pain, loss of power and paresthesia in the left arm. Examination revealed a pulsatile tumor in the left supraclavicular region approximately 1 inch (2.5 cm.) in diameter. It was tense and elastic, with an expansile pulsation. A systolic thrill and bruit were present. The overlying skin was healthy and freely movable. The brachial and radial pulses were absent on the left. The Wassermann reaction was reported to be negative. Roentgenographic examination showed a well developed cervical rib on the left side and a rudimentary one on the right. Above the left cervical rib the faintly outlined shadow of a mass in the position of the subclavian trunk was present. Owing to the patient's advanced age and relative lack of symptoms, no operation was performed.

REPORT OF A CASE

History.—Mrs. H. L., aged 47, was admitted to the New Haven Hospital on July 24, 1935. Her chief complaint was numbness and weakness of the left arm. For approximately a year the patient had experienced occasional pain in the region of her left shoulder. In March 1935 the pain increased in severity. Her entire left arm began to ache, particularly the inner aspect of the upper part of the arm. She noticed a progressive weakness of this extremity and was soon unable to perform such household duties as sweeping, dishwashing and ironing. If her hands were immersed in cold water her left hand and forearm became "dead white" and numb, but when heat was applied to the extremity it slowly regained its normal appearance and feeling. These attacks of numbness and blanching also occurred spontaneously about once or twice a day and lasted about one hour. More recently the left arm began to feel heavy and lifeless between the attacks. No swelling of the arm or cyanosis was ever observed. The patient was admitted to the hospital

7. Quinn, T. G., and Davison, G.: Left Subclavian Aneurysm in Association with Cervical Rib, Brit. M. J. **2**:808, 1934.

for hemorrhoidectomy in 1933, and she stated then that she had noted a small pulsatile tumor above the left clavicle. It was symptomless at that time and sometimes seemed to be absent.

The patient's father, paternal uncle and grandfather all died in their forties of a disease of the kidneys and associated complications. The mother died at the age of 46, after an operation for cancer in the region of the neck.

At the age of 7 the patient had measles and scarlet fever followed by dropsy. She had frequently recurring tonsillitis and had influenza during the 1918 pandemic. In 1908 she was thought to have pleurisy. In 1920 she was hospitalized for two weeks because of blood poisoning following an abscess on the right arm. In 1924, at the age of 36, hysterectomy was performed in another hospital. She was told that the ovaries were full of tumor tissue and might become cancerous. The appendix was removed at the same time.

Review of Symptoms.—Severe headaches, lasting from one to several hours, had been noticed for two or three years. Vision was occasionally blurred. At approximately the age of 15 the patient had repeated attacks of epistaxis associated with the spontaneous appearance of dark lumps in the skin along the course of the large superficial veins. After hysterectomy in 1924 this symptom abated. The patient had an illness diagnosed as bronchitis five years before admission, after which a nonproductive cough had been noticed frequently. Menstruation began at 16 and ceased entirely after hysterectomy in 1924.

Physical Examination.—The rectal temperature was 99.8 F.; the pulse rate, 84; the respiratory rate, 18, and the blood pressure 185 systolic and 110 diastolic (right arm). The patient appeared to be a rather poorly nourished and very apprehensive woman of middle age. Her height was 62 inches (157.5 cm.) and her weight 101 pounds (45.8 Kg.). The positive findings were:

The fundi showed arteriolar constriction. Just above the left clavicle and lateral to the border of the sternocleidomastoid muscle was a smoothly rounded mass, 3 by 3 cm., with a definite, expansile pulsation. No thrill could be palpated, but on auscultation a sharp systolic bruit was heard. The skin and subcutaneous tissues were freely movable over the mass, which was much less prominent when the left arm was elevated. The tumor could be displaced slightly by pressure, which caused pain in the arm.

An occasional coarse, crackling râle was heard over the lower lobe of the left lung. The heart was slightly enlarged to percussion, with the maximum apex impulse in the fifth interspace 8 cm. beyond the left sternal border.

A well healed suprapubic midline scar was present.

The fundus uteri was absent. There were no adnexal masses or tenderness to palpation. The anal sphincters were hypertonic.

The arteries of the right arm were slightly tortuous but normally pulsatile. The left arm, however, was definitely cold and pale; the brachial, radial and ulnar pulses could not be felt, although a weak impulse was detected high in the axilla. There was no evidence of localized muscle wasting in the thenar or hypothenar eminences and no demonstrable motor weakness. Thorough sensory examination was everywhere normal except on the volar aspect of the tip of the fifth finger, where there was diminished sensibility to pinprick, heat and cold. All deep reflexes

were equal and active. Oscillometric readings were carried out on the arms with the following results:

Cuff Pressure, Mm.	Right Forearm	Left Forearm
190	0	0
180	¼	0
170	½	0
160	1	0
150	1¼	0
140	3	0
120	3½	0
100	4	0
80	2½	0
60	1¼	0

Cuff Pressure, Mm.	Right Arm	Left Arm
190	¾	0
180	1	0
160	4	0
140	7	¼
120	8	½
100	8½	½
80	4½	½
60	2½	½

Elevation of the left arm did not change the oscillometric readings.

Studies of the temperature of the skin showed that when the environmental temperature was maintained at 70 F. the surface temperature of the right hand was about 90 F., whereas that of the left hand was 80 F. When the room temperature was raised to 80 F., the skin temperature on the right was stabile at 92 F. and on the left it varied from 83 to 87 F. These findings suggested organic occlusion of the vessels on the left rather than pure vasospasm.

Laboratory Examinations.—The Kahn test was negative. The urine contained no albumin, sugar or sediment. Roentgenographic examination on July 25 (fig. 1) revealed a cervical rib on the left, with a faint suggestion of soft tissue swelling near its distal end. The bronchovascular markings were slightly increased, but the pulmonary fields showed no evidence of infiltration. There was thickened apical pleura on the right. The right costophrenic sinus was shallow and showed pleural thickening. The heart was within normal limits as to size and configuration. The aorta was slightly uncoiled and showed some calcification in the knob. There was no evidence of intrathoracic aneurysm. The right transverse process of the seventh cervical vertebra showed a slight prolongation suggesting a rudimentary rib.

Diagnosis.—A diagnosis was made of arteriosclerosis and hypertension, a cervical rib on the left side and an aneurysm of the left subclavian artery.

Operation and Course.—On August 1 operation was performed with the patient under tribromethanol and ethylene anesthesia. The patient's neck was extended and rotated toward the right, and a left supraclavicular incision was made approximately 12 cm. in length, 3 cm. above and parallel to the upper border of the clavicle. The posterior margin of the sternocleidomastoid muscle was freed from its insertion on the clavicle. After transection of the omohyoideus muscle and

the transverse cervical artery, an excellent exposure of the region of the scalenus muscle was obtained. The tip of the cervical rib was identified between the scalenus anticus and the scalenus medius muscle. Lying on it were the subclavian artery and the lower cord of the brachial plexus, definitely distorted in their course. At the point where the cervical rib impinged on the undersurface of the subclavian artery the vessel was approximately 4 mm. in diameter. Immediately beyond this point the vessel dilated into an aneurysmal sac, which was fusiform

Fig. 1.—Roentgenogram of the upper part of the chest, taken on July 25, 1935.

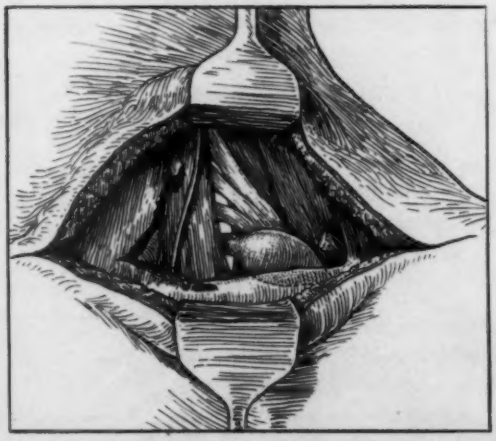

Fig. 2.—Sketch of the operative field (with drapes eliminated).

in outline and measured 2 cm. in its greatest diameter (fig. 2). At the point where the vessel disappeared again under the clavicle it approached a caliber of 8 mm. The aneurysmal sac was slightly but definitely pulsatile. The cervical rib was adherent by dense fibrocartilaginous bands to the upper surface of the underlying first rib. By retracting the brachial plexus upward and outward and the aneurysmal dilatation of the subclavian downward and mediad, the cervical rib was adequately exposed and the distal 4 cm. was rongeured away. After this

procedure the phrenic nerve was isolated from the scalenus anticus muscle, and the latter was severed completely at its insertion on the first dorsal rib. The wound was closed without drainage.

The patient stood the operative procedure well, but on the following day signs of lobar atelectasis involving the lower lobe of the left lung developed. A roentgenogram of the chest taken on August 3 revealed an absence of the left cervical rib except for a small stump at the vertebral end. No pneumothorax was visualized. The left dome of the diaphragm was elevated, and the lower part of the left pulmonary field was definitely opaque. In the lower part of the right pulmonary field there was a slight pneumonic infiltration. The condition in the chest cleared rapidly, and the vital signs were normal again on the fourth postoperative day. The wound healed per primam. During the convalescence there was pain at night in the left elbow and forearm over the distribution of the eighth cervical and the first thoracic nerve. This pain was absent during the day and had disappeared at the time of discharge on August 8.

A follow-up examination on August 17 revealed a definite though slight radial pulsation to be present at the left wrist. Both hands were of normal color and felt to have approximately the same temperature. The patient noticed a distinct improvement in subjective sensation, and she was able to wash dishes for the first time since the previous spring. The operative site was well healed.

She was observed again on October 16. During the first week of the month she had paresthesia in the left arm, which cleared without treatment. Numbness and pain had entirely disappeared. She had gained 2 pounds (0.9 Kg.) in weight. She was using the arm for various kinds of housework, such as sweeping and ironing, without undue fatigue. The palpable aneurysm had not changed appreciably in size.

Oscillometric studies of the left arm were made on that date:

Cuff Pressure, Mm.	Forearm	Arm
190	0	½
180	½	1¼
160	1	1½
140	¾	1½
120	½	1¼
100	½	¾
80	½	½
60	¼	½
40	0	¼

Temperature studies showed the skin of the fingers to vary bilaterally from 85 to 87 F. in an environmental temperature of 70 F.

COMMENT

In regard to diagnosis, Keen[8] wrote in 1907:

Usually the pulsation is visible as well as palpable, and is marked. It is occasionally noted that it is "expansile." Bruit and thrill, one or both, are often present, the latter less frequently than the former. The bruit, however, is not propagated. Neither the thrill nor the bruit seem to be of the true aneurysmal character.

8. Keen, W. W.: The Symptomatology, Diagnosis and Surgical Treatment of Cervical Ribs, Am. J. M. Sc. **133**:173, 1907.

He quoted a letter from Paget to Professor Turner warning against confusion of an abnormally high and easily palpable subclavian artery with a true aneurysm of the same vessel. Murphy,[9] after finding at operation only a slight cylindric dilatation of the subclavian vessel in a patient with cervical rib who presented clinically a large pulsatile supraclavicular swelling, concluded that a diagnosis of aneurysm in this situation was rarely warranted without operative verification.

There is no agreement in the literature as to the proper mode of therapy when aneurysm of the subclavian artery is associated with cervical rib. A study of case records indicates that this type of aneurysm does not tend to increase in size with secondary manifestations of pressure or danger of rupture. If anything, the contrary is true, for occasionally spontaneous thrombosis has been noted as in the case of Billington.[6] The simple application of a pressure bandage to the supraclavicular region has resulted in the clinical disappearance of the tumor in certain cases.[2] According to Keen, in no case prior to 1907 had the vessel been ligated, which he considered wise conservatism. The relatively benign nature of these lesions is well illustrated by the patient of Quinn and Davison; in her case a swelling in the neck had been noticed for thirty years, although no symptoms appeared until a fall one month before the time of diagnosis. It would seem, therefore, that surgical removal of such aneurysms should be advised not as a routine but only for cogent indications. The adherence of the aneurysmal dilatation to the lower cord of the brachial plexus, as in the case of Billington, may be considered a proper indication. It is possible, however, that scalenotomy, as advised by Adson,[10] with or without partial resection of the cervical rib, would have given adequate relief in this case.

The question arises whether local pathologic change in the third portion of the subclavian artery may affect the circulation of the upper extremity unfavorably by reflex effects on the peripheral arteries. Influenced by Leriche's hypothesis that a local pathologic process in an artery may create a focus of hyperexcitability and thus a point of origin for vasoconstrictor impulses mediated through the periarterial sympathetics, Langeron[11] expressed the belief that simple resection of the cervical rib did not suffice to relieve symptoms referable to vasospasm when secondary changes had already occurred in the subclavian artery

9. Murphy, J. B.: A Case of Cervical Rib with Symptoms Resembling Subclavian Aneurysm, Ann. Surg. **41**:399, 1905.

10. Adson, A. W., and Coffey, J. R.: Cervical Rib: A Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus, Ann. Surg. **85**:839, 1927.

11. Langeron, L.: Sur les manifestations vasculaires liées à la présence de côtes cervicales, Paris méd. **2**:43, 1933.

at the point of impingement of the cervical rib. Therefore, in two patients with cervical rib who presented evidences of vascular occlusion of the arm and at operation showed degenerative and thrombotic changes in the subclavian vessel in its third portion, he carried out local resection of the pathologic portions of the artery, in one case combined with resection of the cervical rib. Both patients showed lasting relief from vasoconstrictor crises and healing of trophic disturbances. It might be thought that aneurysmal dilatation alone could act as a focus of irritation and should therefore be excised when scalenotomy or resection of the rib is performed. However, irritation of the sympathetic and sensory fibers present in the lower cord of the brachial plexus by an impinging cervical rib is to us a more satisfactory explanation of the vasospastic phenomena. Newell [12] found microscopic evidences of degeneration in the lower cord of the brachial plexus of a patient with cervical rib. Vasoconstrictor crises, peripheral thromboses and even gangrene of the finger-tips have been observed in cases in which the cervical rib was anatomically so constituted as to impinge only on the lower cord of the brachial plexus and not on the subclavian vessel.[13] These considerations shift the emphasis from the pathologic process in the vessel to mechanical irritation of the brachial plexus, and our decision was to perform scalenotomy and resection of the rib without molesting the aneurysm.

The case reported presents a definite history (familial and personal) of hypertensive vascular disease. Hypertension may have been a contributing factor in the development of the local pathologic process. It is interesting that in all four patients the aneurysm was present on the left side, although three of the four presented roentgenographic evidence of cervical rib bilaterally. The dilatation or aneurysm of the subclavian vessel has invariably been found distal (peripheral) to the actual point of impingement of the vessel and the rib, as in our case. There is no adequate explanation of the mechanism involved in their production beyond the law of hydrodynamics which states that reduction in velocity of a fluid flowing through a cylindric channel is attended by an increase in the lateral or wall pressure.[14] Halsted [3] undertook the reproduction of the condition experimentally. In two dogs he was

12. Newell, R. L.: Cervical Rib with Vascular Complications, Brit. M. J. **1**:782, 1933.

13. Telford, E. D., and Stopford, J. S. B.: The Vascular Complications of Cervical Rib, Brit. J. Surg. **18**:557, 1931. Blair, D. M.; Davis, F., and McKissock, W.: The Etiology of the Vascular Symptoms of Cervical Rib, Brit. J. Surg. **22**:406, 1935. Newell.[12]

14. Babcock, W. W.: Newer Surgical Methods of Treating Diseases of the Vascular System, Am. J. Surg. **16**:401, 1932.

able to produce some degree of dilatation of the abdominal aorta distal to a point of incomplete occlusion by a metallic band and demonstrated a rise in diastolic and fall in systolic pressure beyond the point of constriction.

Within the last month another example of this unusual condition has come to our attention.

A 20 year old waitress was observed during a routine physical examination to present a visibly pulsating expansile tumor in the left supraclavicular fossa. The mass, which was approximately the size of a walnut, was compressible in part. The overlying skin was not adherent and was normal in color and texture. A definite bony prominence could be palpated medial and posterior to the tumor, over which a systolic bruit was present. There was no abnormality in timing or force of the pulses in either upper extremity. Oscillometric readings and skin temperature reactions were within normal limits. There were no trophic disturbances of the fingers or nails. A roentgenogram revealed a well developed cervical rib on the left, which was somewhat larger but otherwise very similar to that of our first patient. There was a soft tissue shadow lateral to the cervical rib in the approximate position of the pulsating tumor. The patient had no symptoms and refused operation after a candid presentation of the problem. In the absence of operative verification, the case can only tentatively be regarded as one of subclavian aneurysm in association with the cervical rib.

ACUTE HEMATOGENOUS OSTEOMYELITIS

CLASSIFICATION OF THE CASES OF ACUTE HEMATOGENOUS OSTEOMYELITIS AS DETERMINED BY THERAPEUTIC INDICATIONS; RESULTS OF OPERATIVE TREATMENT

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NEW YORK

In every case acute hematogenous osteomyelitis is basically composed of two components: (*a*) a general bacterial infection (sepsis, septicemia and bacteremia) and (*b*) a local lesion in the bone tissue. In the treatment of this disease in the early stages the most important item is the general infection. The ultimate outcome, death or recovery, depends entirely on this factor, and the mortality statistics of acute hematogenous osteomyelitis in its early stages reflects accurately the mortality of general bacterial infection. When divorced from the general bacterial infection and in the absence of any fatal complications or associated lesions, the mortality of the local osseous lesion is nil.

The treatment of a local lesion of the bone is a problem by itself. In the presence of a general bacterial infection, the latter naturally, must be taken into account. In the absence of any demonstrable evidence of a general bacterial infection, the method of treatment of the local lesion is to be decided on its own merits, as determined by the pathogenesis, by the biologic and anatomicopathologic development and by the physical characteristics of the total resultant lesion.

In this communication a number of cases are described which illustrate the various clinical groupings into which cases of acute hematogenous osteomyelitis can be placed. The groups are differentiated by the relationship of the general infection to the local lesion, by the magnitude of the general infection, by the presence or absence of complications or associated lesions, by the general nature of the pathologic process of the local osseous lesion and by the presence or absence of a well defined abscess. The object of this is to show that the treatment of acute hematogenous osteomyelitis cannot be standardized except as the indications are furnished by laboratory data.

Until recently there existed an almost universal opinion among both medical men and surgeons that urgency in the treatment of acute hematogenous osteomyelitis was a paramount issue if one wished to avoid fatalities because of the general infection, the inference being that as the general infection was derived from the local lesion of the bone, osteo-

tomy, with or without excision of the diseased area, was necessary in order to remove the focus and so control the bacteremia. It will be shown that except in rare instances the inference is incorrect, because operation on the local focus in the bone does not accomplish this object. Either the patient dies irrespective of the operation, or the character of the postoperative course lends itself strongly to the opinion that the operation has had no inhibitory effect on the general infection.

As a corollary to both of these sets of observations it will be shown that urgency in operative treatment is frequently less necessary and less important than intelligent and watchful observation; that rarely, but more commonly than is generally known and understood, foci of hematogenous osteomyelitis subside completely and spontaneously without going on to the stage of necrosis and sequestration; that, similarly, sequestrated areas of bone can and do become revascularized and become reincorporated with neighboring normal bone tissue in much the same manner as a bone graft does, and that more frequently than is understood among the general medical profession and among surgeons, operation can be entirely avoided.

Also as a corollary to all of these observations and discussions, it will be shown that operative treatment, when necessary, should not consist of an uncontrolled, vaguely planned and hasty, careless or reckless chopping of bone in areas in which the pathologic process is not always perceptible to the unaided eye, in which the boundaries of normal and diseased bone are not visibly differentiated and in which the possibilities for revascularization cannot be foretold. These are ill designed operations which deal ineffectively with the local lesion. Much harm can and commonly does result immediately, due to the extension of the osseous lesion and/or the production of contiguous complications and, subsequently, the retention of factors which make for recurrences and recrudescences of infection or the production of mechanical conditions which prevent healing.

Finally, it will be shown that operation, when necessary, had best be limited to the simplest of procedures, frequently to the mere incision and drainage of abscesses. In all cases the greatest part of the work must be left to nature, so that avascular areas may be given every opportunity to become revascularized, so that as little as possible of the compromised area shall be irrevocably lost and so that the areas of bone tissue which are lost may be allowed to separate completely from the host and be cast off in the form of a foreign body. Then there will be a minimum of recurrences and recrudescences.

It should be recognized that acute hematogenous osteomyelitis is an incident in a general bacterial infection. Therefore, one may not expect or hope that the mortality of the local lesion (i. e., of the osseous

lesion) will be any less than that of the corresponding and accompanying general infection. It may be taken for granted, except when uncontrollable accidents occur, such as secondary hemorrhage, or when fatal complications are present, such as pericarditis and meningitis, that the mortality of the local lesion is nil. If one keeps these two statements in mind and guides oneself accordingly, much confusion will be avoided.

REPORT OF CASES

GROUP 1.—*Cases in which operation of any kind can be avoided: Subgroup A. Cases with spontaneous early retrogression of the osseous lesion.*

CASE 1 (chart 1).—A young boy was admitted to the hospital with an illness which began one week previously, with pain in the region of the right hip and inability to bear weight on the right leg. The results of the general physical examination were entirely negative. In the region of the right hip there was a tender, hot, red swelling, about the size of the palm, the lesion extending around to the right inguinal region. Clinically, there was no doubt that the pain and tenderness were referable to the bone. There seemed to be evidence, also, of a certain amount of effusion in the right hip joint. The temperature on admission was 104 F. The patient was referred to me for operation for osteomyelitis of the upper end of the femur. However, a conservative policy was followed, and on the day after the patient's admission to the hospital the temperature fell to fairly normal levels, and the local signs improved progressively and markedly and finally disappeared altogether. One week later the patient was discharged from the hospital entirely well.

A blood culture taken on the day of admission was sterile. Roentgen examination made on the fifth day after admission to the hospital showed evidences of a lesion in the neighborhood of the right trochanter, extending upward into the neck, which was undoubtedly an inflammatory process in the substance of the bone.

This case illustrates well the fact that not all forms of osteomyelitis necessarily go on to the stage of suppuration or necrosis of tissue. It must undoubtedly be true that in some cases infection of bone tissue will develop to a certain extent only and will then promptly retrogress to the normal, as is illustrated by this case. In such cases treatment is not needed.

The following case is a typical case of acute hematogenous osteomyelitis. The entire clinical history is available in full, together with complete laboratory data. Only conservative therapeutic measures were employed, and no operation was performed. The patient recovered spontaneously from the acute osteomyelitis and the accompanying general blood infection, with a minimum of structural deformity and with practically no loss or disturbance of normal function. New therapeutic points of view are illustrated by this case which should be stressed. Emphasis is being placed on the criteria on which treatment is based and on the dominating value of laboratory data, especially the blood culture and roentgenographic studies.

Subgroup B. Cases in which the osseous lesions go through a complete development beginning with the stage of bacteremia and continuing through necrosis, sequestration and exfoliation of bone tissue without the necessity for operation and with spontaneous healing and recovery.

Case 2 (chart 2).—A boy aged 10 years had a congenital cardiac lesion. In January 1927 he had a small furuncle on the chin, which was opened in the outpatient department of the hospital and healed thereafter. The boy was admitted to the hospital one month later with the history that five days prior to his admission he had been kicked in the side, in the general neighborhood of the hip; since then there had developed fever, pain in the general region of the hip and a limp on walking, and all of these signs had progressively increased. On the second day of

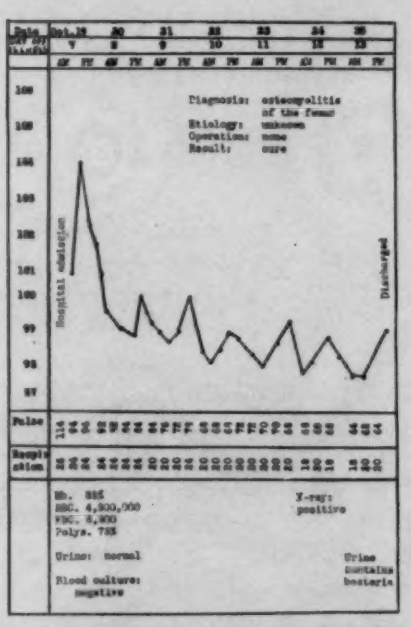

Chart 1.—Clinical record of the patient in case 1. The data presented here are representative of those which are recorded in similar cases, classified as group 1, subgroup A.

the illness the patient had a severe nosebleed. During the course of the illness up to the time of his admission there had been no chills, but he had high fever and became delirious, his temperature on admission to the hospital being 105 F.

Physical examination revealed a very sick, delirious child, in a markedly toxic condition, with a high temperature, signs of a cardiac lesion, a palpable spleen and local objective signs of an infection in the neighborhood of the right hip. It was obvious that a hematogenous infection secondary to the furuncle of the chin was being dealt with. The rôle of the trauma to the side was purely a contingent or contributory one and determined the localization of the secondary focus by creating in some way a locus minoris resistentiae. It was assumed that the infection was seated somewhere in the skeleton in the neighborhood of the right hip, but owing to the diffuseness of the signs of the local lesion and to the lack of any evidence

which would enable one to localize the seat of the infection definitely and also because of the extremely serious condition of the child, a conservative policy was followed.

A blood culture made on the day of admission showed 48 colonies of Staphylococcus aureus. The white blood count was 8,600, and the polymorphonuclear count, 87 per cent. The urine was normal. A roentgenogram of the entire locality was normal also.

During the following week the temperature gradually came down to a lower level, as can be seen in chart 2. The signs of general infection improved markedly, and the local signs improved to such an extent that it was evident to anybody that no operative procedure was necessary. On the eighth day of the illness a blood culture showed 10 colonies of Staph. aureus; on the tenth day the number had decreased to 2 colonies, and on the eleventh day there was only 1 colony of Staph. aureus per cubic centimeter of blood cultured. On the seventeenth day of the illness the blood culture was sterile, and it remained so thereafter.

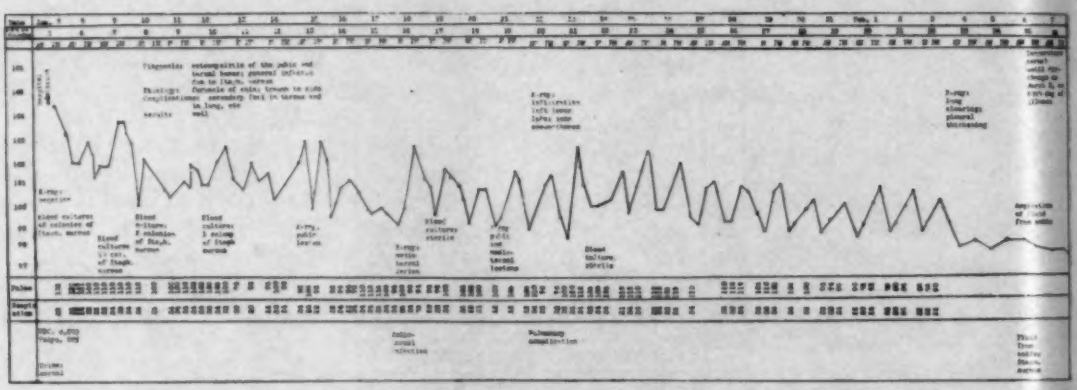

Chart 2.—Clinical record of the patient in case 2. The data presented here are representative of those which are recorded in similar cases, classified as group 1, subgroup B.

Repeated roentgenographic studies demonstrated that the lesion which was present in the neighborhood of the hip was specifically a lesion in the ascending ramus of the pubis of the same side.

On the sixteenth day of the illness pain developed in the right ankle. About three days later it was established that a lesion was present in the metatarsal bones and joints of the foot. The lesion in the ankle was well marked, and there were many times during the course of its development when it seemed as if the abscess, which was undoubtedly present, would burst through the skin and discharge. This, however, it never did. On the thirty-ninth day of the illness, for purposes of study, the lesion on the foot was aspirated, and the fluid obtained was found to contain Staph. aureus. This lesion was treated most conservatively and was never operated on.

On the twenty-second day of the illness the temperature rose to 103 F. There was precordial pain, and a cough developed. Three days later there was a well established consolidation of the left lung. This was confirmed by roentgenographic examination. On the thirty-fifth day of the illness the pulmonary consolidation was seen to be rapidly clearing, and all that was left was a slight amount of pleural thickening.

On the sixty-second day of the illness the patient was discharged from the hospital, free from fever and generally in good condition, with no signs referable to the hip or the pubis and with the foot still swollen but with the condition rapidly subsiding. He was discharged from the hospital with a plaster cast on his foot.

The patient was readmitted to the hospital a number of times thereafter for various complaints. The second admission was for the purpose of renewing the plaster cast. During his third admission a small sinus formed in the perineal region, with practically no inflammatory reaction around it, and from this sinus an inconspicuous fragment of bone was discharged. This occurred three months after the onset of the illness. During the patient's fourth admission to the hospital (1928) an infection developed in the upper part of the right arm, which subsided spontaneously. No osseous lesion could be demonstrated by a roentgenographic examination. During his fifth admission to the hospital (1929) a lesion was demonstrated in the upper end of the left tibia roentgenographically. Treatment was not instituted. Seven years after the onset of this illness and five years after the last admission to the hospital, the patient died because of the cardiac condition, and during the five intervening years he had no signs referable to the bones of the skeleton or to his preceding infection. As stated previously, the cardiac condition was congenital and had nothing whatever to do with the osteomyelitis or with the general infection.

This case report recounts the history of the development and course of an acute general infection for which the patient was presented for treatment at the stage when an acute osteomyelitis was developing in one of his bones. During the entire clinical course events occurred which were the exact counterpart of events which are being seen repeatedly in similar cases of general infection with secondary foci in the bones and other organs and tissues of the body in which operations are being done and are being repeated for the foci in the bone on the theory that unless operation is done the patient will die of the general infection or that the osseous lesions cannot and will not undergo spontaneous resolution and healing. The fact that operation was not done in this case would seem to indicate that a patient with acute osteomyelitis and general infection, such as this patient had, can recover spontaneously and that operation is not always necessary for the control of the general infection (bacteremia) or for the control and healing of the foci in the bone.

In this patient subsidiary foci developed in other parts of the body (the lung, the upper part of the arm and the tibia). The question arises as to the relationship of these other foci in the pathologic development of the disease. As I have described in my book,[1] each focus in the bone can theoretically act as a secondary point of distribution, so that it is possible (though relatively unlikely) that different crops of lesions may develop, which I have classified as lesions of the second and third order, etc. It might possibly be said that failure to operate on and

1 Wilensky, A. O.: Osteomyelitis: Its Pathogenesis, Symptomatology and Treatment, New York, The Macmillan Company, 1934.

eradicate the first of the secondary lesions (in this case the lesion in the ischiopubic ramus) may possibly have allowed the latter to develop to the point where it would act as a secondary point of distribution and through the medium of the consequent secondary bacteremia produce lesions of a second order (in this case, the lung, the upper part of the arm and the tibia).

In this case the pulmonary lesions developed at a point of time relatively close to the onset and development of the primary bacteremia derived from the furuncle on the chin. The lesion on the tibia was discovered approximately two years after the onset of the illness. The biologic characteristics of this lesion as deducted from its morphologic appearances (i. e., that of a Brodie abscess) indicate that at the time of observation it had undergone a period of development which in every one's experience could easily have occupied the space of the intervening two years. The origin of this lesion, too, must therefore be referred to a point in time coincident with the presence of the original bacteremia. The available evidence seems to point strongly to the opinion that under such circumstances all of the foci are to be referred to the primary lesion and are to be considered as secondary lesions of the first order. In addition, when a secondary focus acts as a secondary point of distribution, there are, usually, clinical evidences in the given provocative focus of increased or reawakened pathologic activity. No such clinical fact was observed in this case.

The lesion on the upper part of the arm occurred approximately one year after the origin of the osteomyelitis. There was no clinical evidence of any reawakening of activity in the pubic lesion. As a consequence, there was no reason to connect this infection with the primary infection, and, in addition, it was possible that some wound or abrasion of the fingers or hand might have led to a secondary lymphangitic localization in the arm. In view of these facts, the relative position of this lesion in the total picture is in doubt, and possibly there was no connection between the two.

One should not deduce from this case that every person with acute osteomyelitis of hematogenous origin should be or can be treated in this most conservative manner. There are times and occasions when such a policy would invite disaster. The value of this illustrative case lies in the demonstration of the fact that conservatism can be practiced with safety under well regulated and intelligent observation, and, as experience is gained, more and more frequently; that the clinical course of the illness is not influenced to the extent hitherto believed by early or by any operation, and that there are great advantages to conservatism, when it can be practiced, for which radicalism offers no substitute or any advantage, either from the point of view of the period of morbidity and incapacity or relating to anatomic structure and morphology or

to the appearance of the surface and the external contour, or from the point of view relating to the appearance of other foci or even from the point of view of saving life.

GROUP 2.—*Cases in which the general infection is the paramount factor and determines the fatal end-result.*

CASE 3 (chart 3).—A boy aged 5 years was admitted to the hospital with an area of infection surrounding the right clavicle and with the general signs and symptoms indicating one of the most profound general infections of the hyperacute type which I have ever seen. At the time of his admission the child was in a stupor. In spite of the fact that it was well realized that operation directed to the local focus in the right clavicle would probably be of no avail, the condition seemed most suitable for a total excision of the involved bone, and the latter operation was done forthwith. Nevertheless, this had no effect on the clinical course of the illness, and the patient died.

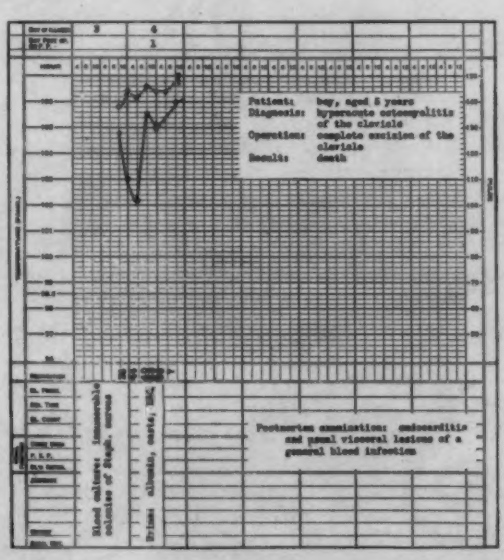
Patient: boy, aged 5 years
Diagnosis: hyperacute osteomyelitis of the clavicle
Operation: complete excision of the clavicle
Result: death
Blood cultures: innumerable colonies of Staph. aureus
Urine: albumin, casts, blood
Postmortem examination: endocarditis and renal visceral lesions of a general blood infection

Chart 3.—Clinical record of the patient in case 3. The data presented here are representative of those which are recorded in similar cases, classified as group 1, subgroup B. The solid line indicates the temperature record; the dotted line, the pulse record.

This case illustrates well the futility of operative treatment even of the most radical and maximum type (i. e., amputations and excision of bones in toto) in cases of overwhelming general infection with foci in the bone in which the local lesion is, manifestly, an incident—and a negligible one at that—in the total clinical complex. Occasionally it happens that one is tempted to operate in cases of this type because of extraordinary conditions or associated factors or at the insistence of the patient's family. The effort will, however, be fruitless as death occurs promptly, because of the general infection (bacteremia) and not because of the local lesion.

Compare this case and its chart with the composite chart (chart 4) of the temperature records in four similar cases. Note that the general infection is so overwhelming that the fatality occurs at the peak of the temperature curve in two of the cases. After forty-eight hours the resistance of the patient is completely broken down, so that the temperature reaction is destroyed, and death occurs with the temperature at a low point. This happened in the other two cases.

Case 4 (chart 5).—Two weeks after an attack of acute tonsillitis and the appearance of several cutaneous furuncles, a youth 20 years of age was admitted to the hospital with a well marked general staphylococcic sepsis and a local lesion in the neighborhood of the knee. On the sixteenth day of the illness some clear greenish straw-colored fluid was obtained from the knee. Cultures of the fluid did not yield any organism. On the eighteenth day of the illness an abscess in the lower and posterior part of the thigh extending into the popliteal space was opened and drained. On the same day a metastatic focus was observed in the sternoclavicular joint.

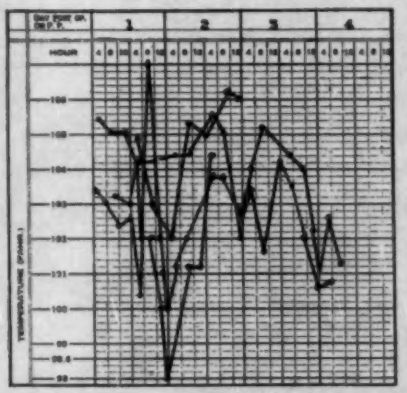

Chart 4.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis similar to case 3 (chart 3).

The operation did not cause any appreciable change in the temperature reaction or other general observable clinical facts, and the general infection (sepsis) apparently continued not only unchanged but in increasing intensity, as shown by the blood culture made on the twenty-second day of the illness, when large numbers of colonies were grown in the culture plates. Death occurred on the twenty-sixth day of illness and six days after operation. Postmortem examination showed the osteomyelitic focus in the femur.

This case illustrates the effect of operation on a patient with acute osteomyelitis and a general infection, the severity of which was at first judged to be of moderate grade. It again demonstrates the fact that the local focus in the bone is not the most important factor in the total clinical picture. Contrary to the usual experience, the fixation abscess, which developed in association with the local lesion in the

bone, did not minimize the general infection and its demonstrable bacteremia; instead, the bacteremia became exaggerated, and incision of the abscess made little difference in the observable phenomena of the general infection. The experience also teaches that while incisions of frank abscesses are always indicated, one must not always expect too much from the procedure.

Compare the chart in this case with the composite chart (chart 6) in which are the temperature records from four other cases of acute hematogenous osteomyelitis of severe, though not fulminating, grade of general infection. Operation was performed in three of the cases. The blood cultures were positive in all. Death occurred in all the cases.

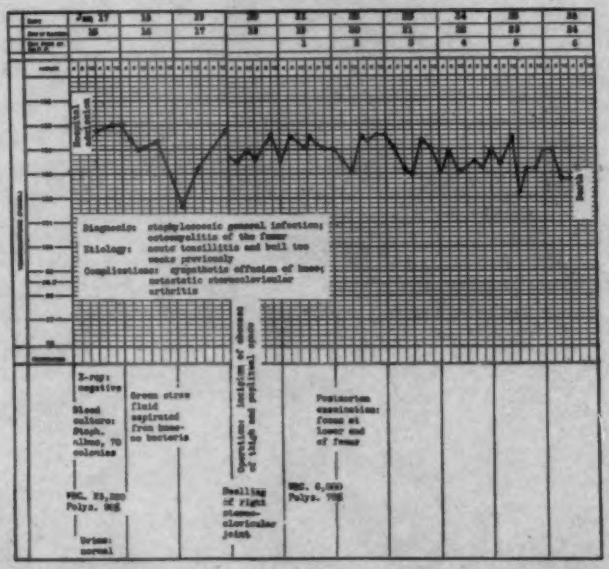
Diagnosis: staphylococcic general infection; osteomyelitis of the femur
Etiology: acute tonsillitis and boil two weeks previously
Complications: apparently effusion of knee; metastatic sternoclavicular arthritis
Operation: incision of abscess of thigh and popliteal space
Blood culture: Staph. albus, 70 colonies
Gross: clear fluid aspirated from knee; no bacteria
Urine: normal
Swelling of right sternoclavicular joint
Postmortem examination: femur at lower end of femur
Death

Chart 5.—Clinical record of the patient in case 4. The data here are representative of those which are recorded in similar cases, classified as group 2.

Note that it did not make any difference whether or not operation was performed so far as the postoperative clinical facts and the end-result were concerned, and, again, that the local lesion is a negligible factor. The usual duration of an illness with this grade of infection is about one week.

GROUP 3.—*Cases in which the general infection becomes controlled and the end-result depends entirely on the local lesion and/or any intercurrent complication or associated lesions: Subgroup A. Cases with fatal end-results because of complications or associated lesions.*

CASE 5 (chart 7).—A woman 23 years of age, in previous good health, was admitted to the hospital with the history that three days before her admission the

left lower posterior molar was extracted because it contained a cavity and was impacted and had given rise to a great deal of pain. The dentist who extracted the tooth sutured the wound in the mucous membrane. Afterward an infection developed on either side of the alveolar process in the pretonsillar space and in the submaxillary space on the same side.

The results of the general physical examination were negative. Locally, there were marked swelling, redness and tenderness of the left side of the face and neck. An area of fluctuation was present, and inside the mouth there was a gangrenous infection surrounding the posterior end of the alveolus and in the tonsillar and pharyngeal space. The urine contained albumin but was otherwise normal. The blood culture was sterile. The blood count showed the following: hemoglobin, 64 per cent; red blood cells, 4,370,000; white blood cells, 47,000; polymorphonuclear cells, 95 per cent; band forms, 52 per cent; lymphocytes, 1 per cent; mononuclear cells, 1 per cent, and myelocytes, 3 per cent.

The patient was in the hospital for fifteen days, during which time incisions were made internally in the mouth and externally in the neck for the drainage of collections of pus in the submaxillary triangle and in the interior of the mouth in the pretonsillar space. The posterior parts of the alveolar border of the left side

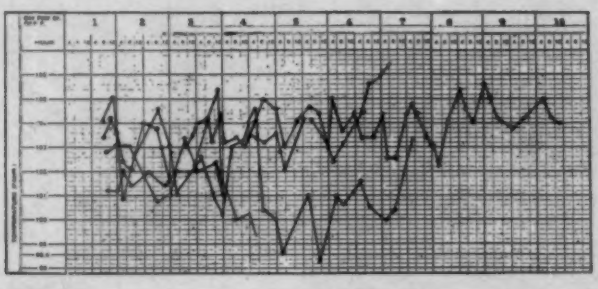

Chart 6.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis of severe, though not fulminating grade of general infection.

of the lower jaw were bared and necrotic. The abscesses were characterized by a fetid gangrenous infection, causing necrosis of the entire fascial sheath of the neck, including the deep and superficial cervical fascia and the deep layers extending downward from the latter into the substance of the neck. The infection extended to the right side of the neck and downward into the thorax following the fascial planes, and an abscess developed in the upper anterior portion of the right side of the mediastinum. A focus was also present in the lower lobe of the lung on the same side. It was necessary to revise the operative wounds several times. These findings were abundantly confirmed by roentgenographic studies.

In the last two days of the patient's life there were considerable and increasing oozing and active hemorrhage from the right side of the neck, which was controlled only partially by packing. In spite of the fact that the general condition of the patient was supported by transfusions of blood and in all other possible ways, the patient grew steadily worse and finally died at the end of the indicated period, death undoubtedly being hastened by the continuous hemorrhage.

This case illustrates the fact that patients frequently recover from the original general infection (bacteremia) and then other complications

or associated lesions develop, from the effects of which a fatality occurs. In such circumstances the lesion of the bone, except as it may cause or lead to the complicating fatal lesion (joint infection, hemorrhage and mediastinitis), plays no part in the eventual issue.

GROUP 3.—*Cases in which the general infection becomes controlled and the end-result depends on the local lesion and/or any intercurrent complication or associated lesion: Subgroup B. Cases in which both of these factors become controlled and recovery follows.*

CASE 6 (chart 8).—In an adolescent boy the extraction of a tooth was followed by a dento-alveolar abscess. About one week later a focus developed in the left radius. At the time of his admission to the hospital the patient was moderately ill,

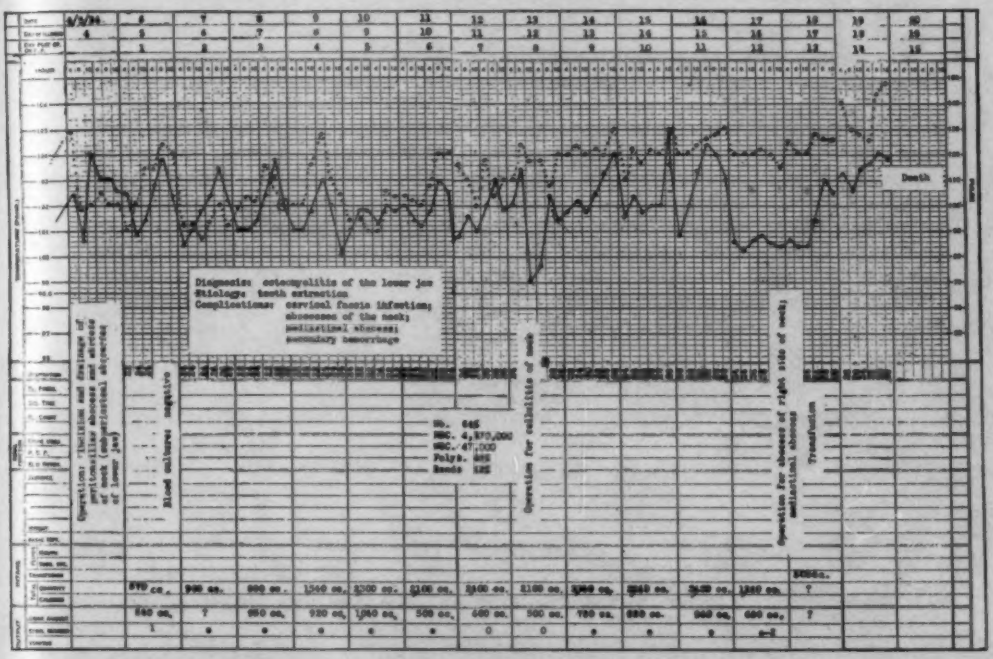
Diagnosis: osteomyelitis of the lower jaw
Etiology: tooth extraction
Complications: cervical fascia infection; abscesses of the neck; mediastinal abscess; secondary hemorrhage
Death

Chart 7.—Clinical record of the patient in case 5. The data presented here are representative of those which are recorded in similar cases, classified as group 3, subgroup A. The solid line indicates the temperature record; the dotted line, the pulse record.

but the blood culture taken before the operation was sterile, and osteotomy was done immediately. The visible signs of the local infection of the bone were definite and well marked. There was a good deal of edema of the periosteum; the bone tissue and the marrow were distinctly inflamed, and there was diffuse suppuration but no distinct abscess. Blood culture made directly after operation showed four colonies of Staph. aureus for each cubic centimeter of blood cultivated. The pus contained the same organism.

On the fourth postoperative day only one bacterial colony to the cubic centimeter of blood developed in the culture plates. A similar result was obtained on the sixth postoperative day. On the latter day, also, a counterincision was made for the purpose of improving drainage.

On the twelfth day after operation pain and tenderness were noted in the region of the left kidney, and pyuria of moderate extent was present. The urine contained Staph. aureus. This was associated with an increase in the temperature. On the fourteenth and fifteenth days after operation the blood cultures were sterile.

An increase in the temperature on the twenty-first day was associated with an arthritis of the left elbow, for which it was necessary to drain the joint.

After the thirty-third day after operation the temperature was normal, and the patient was discharged from the hospital.

This case illustrates the following facts: 1. A complete osteotomy did not improve matters generally.

2. It did not lower the temperature or the pulse rate.

Note especially in this case that so far as the local and general symptoms are concerned, operation had no effect which could be distinguished clinically. This case was one of my earlier ones, seen at a time when I was not so sure of my ground, so that operation was

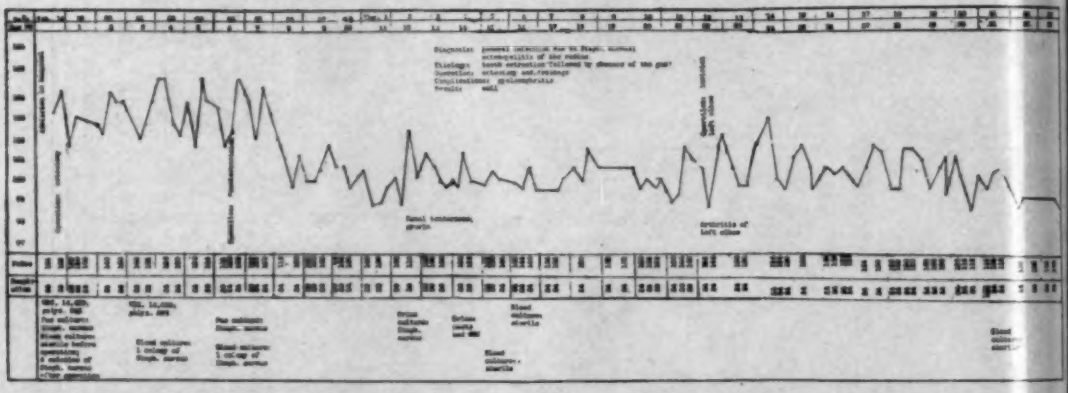

Chart 8.—Clinical record of the patient in case 6. The data presented here are representative of those recorded in similar cases, classified as group 3, subgroup B.

performed. I feel sure that if such a case would present itself today that I should not operate so precipitously; in view of many experiences since, it seems not at all out of the way to think that in this instance the focus would have controlled itself spontaneously and undergone cicatrization and healing without operation of any kind.

Compare chart 8 with chart 9. The latter is a composite chart containing the temperature records obtained in three cases of acute hematogenous osteomyelitis of the ordinary grade and type. The blood cultures were positive in two of the cases and negative in the third. All three patients recovered. Two were operated on during the first week of their stay in the hospital, and the third was not operated on. Note how closely the three temperature curves correspond irrespective of operation. It would not be correct to say that operation had any

effect on the general infection, as evidenced by the temperature curve; the general symptoms and local manifestations corresponded closely to the temperature curve and corroborate this view.

In discussing case 4 (chart 5), it might have been said that the reason no improvement followed the simple incision of the subperiosteal abscess was the failure to perform osteotomy of a more or less radical type and drain the marrow cavity. Case 6 (chart 8) shows that osteotomy did not improve matters in any way and that following operation the condition in each case followed a comparable course. Compare the record of cases 4 and 6 with the composite record in chart 10. The latter is a record of four patients who were treated by various methods. Note how closely the temperature curves correspond. Compare charts 9 and 10. The curves are similar in spite of the fact that they were made in all kinds of cases: those in which operation was performed and those in which it was not and cases in which treatment consisted of simple incision of an abscess and of osteotomy. The comparison shows

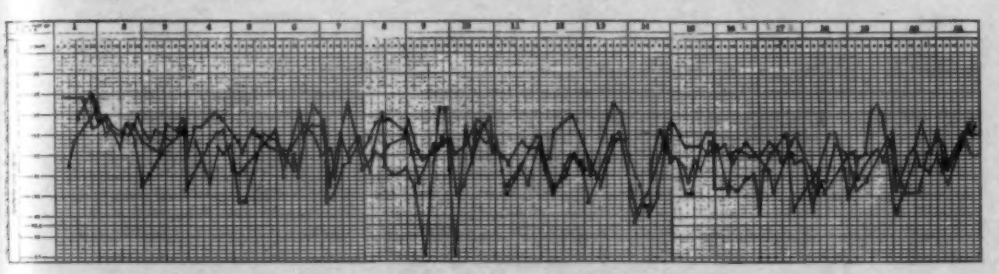

Chart 9.—A composite chart of the temperature records in three cases of acute hematogenous osteomyelitis of the ordinary grade and type.

strongly that the general infection in all these cases is the paramount factor. Recovery occurred in the cases represented in charts 9 and 10.

3. The blood culture became positive after operation.

This is a danger to which one lays the patient open when the seat of the lesion in the bone tissue is cut into with chisel and mallet, because bacterial distribution is mechanically produced from the fixation point in the bone. It is a danger which may not be ignored, and I am sure that it causes more frequently than one cares to admit those recrudescences and exacerbations of infection which commonly determine a fatal issue when previously it had seemed that recovery would eventually follow.

4. Operation did not prevent the appearance of other secondary foci.

Recent discussions regarding this point have been limited to two points of view: (*a*) whether the subsequent secondary foci are tributary to the original primary lesion or (*b*) whether they are referable to the focus in the bone acting as a secondary point of distribution. Theoreti-

cally, each mechanism is possible. Practically, it is an established fact that most of the secondary lesions occur relatively closely to the time of appearance and development of the original primary lesion, and, as far as one can see, there are no evidences in the osteomyelitic lesion of any extraordinary assumption of activity immediately previous to or at the time other secondary lesions make their appearance. As far as this reasoning goes, it would seem correct to assume that certainly in the greatest number of the cases all of the secondary lesions should be referred to the original primary lesion.

In this case osteotomy was immediately followed by the appearance of a bacteremia of small magnitude. This alters matters considerably, and it is altogether correct to say that secondary lesions which appeared subsequent to the establishment of the bacteremia could most likely be due to it. Such a possibility would point out a distinct disadvantage to osteotomy in the early stages of the osseous lesion. (Compare with item 3.)

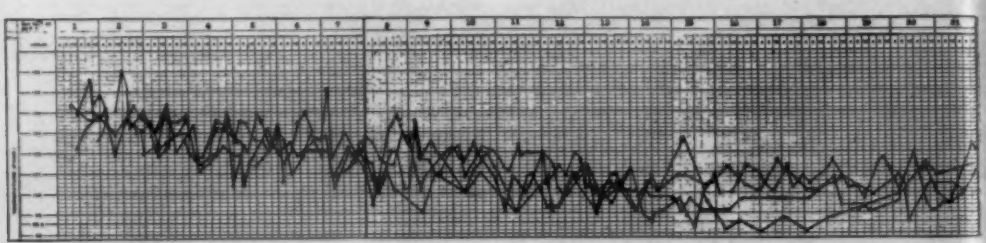

Chart 10.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis in which various methods of therapy were used.

5. Locally, operation was followed by infection in the neighboring joint, by subsequent deformity and by eventual loss of function and disability in the joint and limb.

Arthritis in a joint adjacent to a focus of osteomyelitis might be a natural complication and occur spontaneously. On the other hand, assumption of activity in the focus in the bone might cause spreading of the lesion and secondary involvement of the joint, or the joint might be secondarily infected mechanically during the operative manipulations when the anatomic conditions are appropriate. The thoughtful person would immediately recognize the importance of a policy of noninterference when the local and general signs point to the possibility of avoiding osteotomy.

GROUP 4.—*Cases illustrating the usual case in which the general infection becomes controlled and the end-result depends entirely on the local lesion in the bone.*

CASE 7 (chart 11).—A young child had otitis media and a complicating mastoiditis for which operation was performed. The blood cultures were negative on three occasions. On the sixth day of the illness the blood cultures contained nonhemolytic streptococci, and a thrombosis of the lateral sinus was recognized; the usual operation was done. A remittent fever continued; on the fifteenth day of the illness the blood culture was negative, and a focus in the femur was recognized. Osteotomy was done on the twentieth day of the illness. Subsequently the temperature ran at lower levels and after several weeks came down to normal. The patient was discharged from the hospital on the seventy-first day.

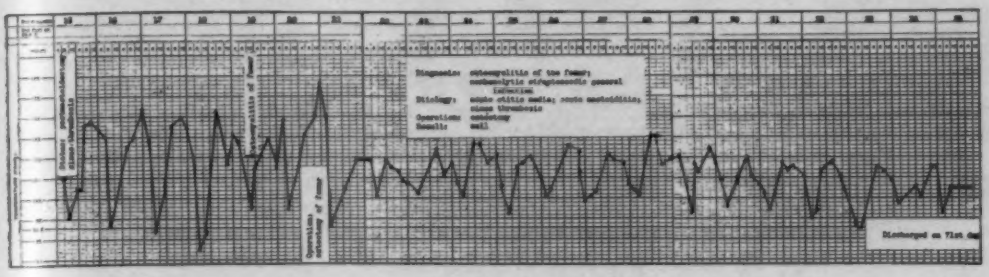

Chart 11.—Clinical record of the patient in case 7. The data presented here are representative of those which are recorded in similar cases, classified as group 4.

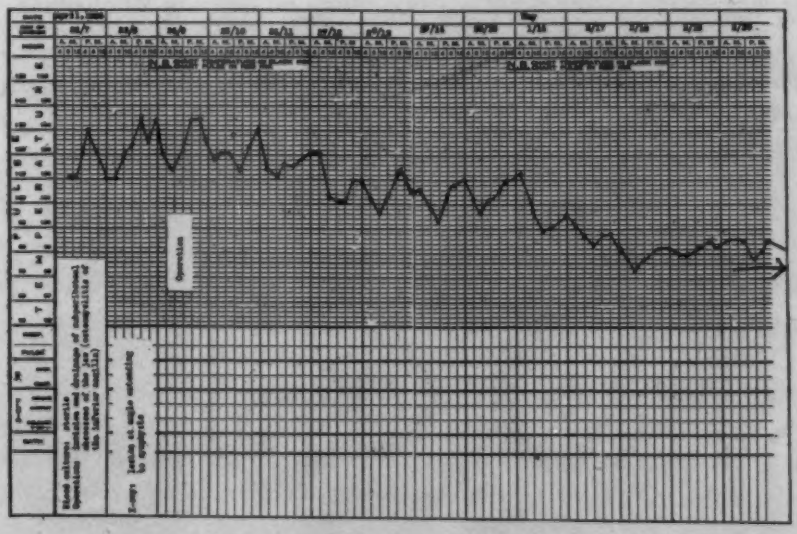

Chart 12.—Clinical record of the patient in case 8, group 4.

CASE 8 (chart 12).—For the usual symptom of pain in one of the teeth of the lower jaw, an extraction had been done about one week previous to the admission of the patient to the hospital. The socket was "lightly" packed. Thereafter progressively increasing pain developed in the lower jaw, the tissues about the jaw began to swell, the swelling becoming more prominent below the ramus of the jaw in the submaxillary triangle. Several incisions were made in the gingivolabial fold by the attending dental surgeon. Pus was not obtained, but the swelling and pain continued to increase.

At the time of the patient's admission, a well defined abscess was present in the submaxillary triangle. A culture of the peripheral blood was sterile.

The submaxillary abscess was incised and drained. Nothing was done to the bone itself nor to any of the teeth. Thereafter the mouth was cleaned regularly with antiseptic washes, and the wound was dressed and cared for in the ordinary surgical way. Under this regimen the amount of discharge lessened and finally became nil; several small and inconsequential sequestrums were discharged from the wound. The wound itself gradually contracted and finally closed and remained closed.

At the peak of development of the pathologic lesion, the roentgenographic studies showed a process involving the horizontal ramus of the lower jaw, extending from near the angle up to the symphysis and across the median line. Although a good deal of destruction was apparently visible in the roentgenogram, nevertheless much revascularization must have occurred because of the inconsequential smallness of the sequestrums, which were discharged.

The cosmetic and functional results are excellent, and there is normal mobility and dental apposition.

The case illustrates the advantages of conservatism when radicalism would lead to unnecessary destruction and loss of bone tissue, to morphologic changes and unnecessary and disturbing anatomic deformity and to disfigurement of the original external contour. Loss of function is prevented (or minimized) because joints are not involved and because the formation of an involucrum is held down to a minimum.

SCIATIC PAIN AND ITS RELIEF BY OPERATIONS ON MUSCLE AND FASCIA

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It has long been known that in many cases continued pain referred to the course of the trunk of the sciatic nerve or to the field of distribution of its two main components, the common peroneal and tibial nerves, the pain may be due to extrinsic pressure by a neoplasm or an infiltration either within the pelvis or outside of it; that the pain at times is caused by a new growth within the spinal canal or by organic disease of the radicles beyond the cord proper; that it is sometimes consequent on disease of the lumbar segment of the spine, and that it may be due to inflammatory disease of the nerve itself, as manifested by those clinical signs on which one must rely, as elsewhere, for the recognition of such neuritis. By these signs is meant impairment of the motor power or disturbance of sensation, either superficial or deep, as well as alteration of the reflexes. From the field of the present discussion it is, however, my purpose to exclude this group of lesions, together with other lesions of an essentially acute and more or less evanescent character. Whatever difficulties they may present, they are involved in no significant obscurity. Quite apart from all of these disturbances is a kind of sciatic pain which may exist for months or years, having irregular remissions or intermissions, but having at the end of such long periods none of the evidences of organic disease of the nerve before mentioned, save perhaps an alteration or absence of the achilles tendon reflex and muscular wasting of an appreciable degree. This type of sciatic pain presents a problem which presses for solution in a manner the more poignant because of the element of chronicity. An orthopedic surgeon is likely to see a patient with sciatic pain only after he has run the gamut of physicians, spas, cultists and downright quacks. Not a few of these patients are in a desperate state of mind and morale. These are the ones who have been told that they have "neuralgia," and their own despair is at times almost equaled by that of the well intentioned medical men who have tried in vain to help them. The term "ischias," or "sciatica," was first used by the Neapolitan anatomist, Cotugno, in 1764. One hundred years later, a notable monograph

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appeared on the same subject by the Parisian clinician and teacher, Lasègue. It is worthy of comment that both Cotugno and Lasègue considered sciatica to be:

> . . . a disease and not a functional trouble; it has therefore, a course which is peculiar to it. To represent it simply as a series of attacks of pain is to explain it very badly.

Cotugno considered it due to a dropsy of the nerve sheath. This was, however, pure ratiocination without demonstration. It is interesting, however, that he compared the symptoms to similar ones within the range of the brachial plexus. The similitude was approved by Lasègue, and I shall have occasion to refer to it again.

THE LASÈGUE SIGN

At this juncture, I ask indulgence if I dwell for a moment on the Lasègue sign. As described by Lasègue, it is characterized by pain which is felt either along the back of the thigh or in the region of the sacrosciatic notch when the patient's knee is extended after he has fully flexed the hip joint. While it may be called forth equally well by flexion of the hip after the patient has fully extended the knee, this sign should not be considered synonymous with mere limitation of so-called "straight leg raising." The latter, betokening spasm or contracture of the hamstring muscles, is often present in association with lesions of the lumbar portion of the spine and in such instances without being accompanied by pain in the regions before mentioned. By many writers, including some recent ones, the explanation of the Lasègue sign is easily found in the stretching of the sciatic nerve. However, it is well known that nothing like stretching of the nerve takes place in this maneuver until the hip has been flexed well beyond 90 degrees, a point which is never even approximated in the patient who has a positive Lasègue sign. Moreover, spasm of the hamstring muscles in disease of the lumbar portion of the spine not only is likely to be painless, except possibly in the spine itself, but is apt to occur bilaterally. On the other hand, it is not unusual to find a contralateral Lasègue phenomenon. By this is meant that when the Lasègue maneuver is carried out on the sound side pain is thereby called forth on the affected side. Many patients with sciatic pain are found to have a negative Lasègue sign. Grossman and Keschner[1] in 1929 reported the results of the clinical analysis of a large series of cases of sciatic pain. Their group I was made up of cases in which the pain was obviously to be ascribed to an organic lesion of the nervous system.

1. Grossman, Morris, and Keschner, Moses: The Sciatic Syndrome, Arch. Neurol. & Psychiat. **21**:398-412 (Feb.) 1929.

Their group II consisted of 267 cases in which no organic cause for the pain could be established; in 118 of these cases, or 44 per cent, the Lasègue sign was negative. Disregarding my own and much smaller series of recorded cases in which the proportion of positive Lasègue response is much larger, these figures are impressive. Since the group is thus divided into two large categories, an explanation is called for if one is to regard the Lasègue sign of important significance, and the figures themselves would indicate that one should. Grossman and Keschner's group II*b*, consisting of 201 cases, represents cases in which there are some indications of an organic change in the nerve. Of these, the Lasègue sign was negative in 43 per cent, whereas in 55 per cent there was a disturbance of the knee jerk. Since the innervation of the quadriceps muscle is entirely outside of the sciatic field, this is important. The segmental innervation of the sciatic field is the fourth and fifth lumbar segments and the first, second and third sacral segments, whereas that of the femoral nerve is the second, third and fourth lumbar segments. Both on anatomic and on clinical grounds, therefore, does it not seem proper to consider these groups of cases separately? In this discussion I shall be concerned only with the situation as it is restricted to the sciatic field. The percentage of cases in which the Lasègue sign is positive and in which the manifestations are found entirely within the sciatic field is sufficiently large to warrant their being placed under a rubric of their own. I have felt for some years that this fact called for an explanation and definition such as had not yet been given. Furthermore, in my own experience, no patient whose reaction to the Lasègue sign was positive and whose symptoms were entirely within the sciatic field has failed to be relieved, even though only temporarily, by means of traction to the extremity made with the hip slightly flexed and in abduction of from 15 to 20 degrees. This appeared to point to a muscular element, even though not certainly.

ANATOMIC RELATIONSHIP OF THE PYRIFORMIS MUSCLE

Anatomic study brought forth the peculiarly close relation between the pyriformis muscle and the trunk of the sciatic nerve which is remarked by most anatomists, even though they do not ascribe any practical importance to it. In 1932, in collaboration with Vinke, an anatomic and mechanical study was undertaken with a view of finding a rational explanation. An experimental method on living animals was obviously impossible. Not even the anthropoid apes have an anatomic arrangement of the sciatic field similar to that of man, and information concerning the psychic response to pain would be altogether denied us. The result of our study on fresh cadavers and in

the dissecting room was published in 1934.[2] We found that Yeoman [3] in 1928 had published the first reference to the pyriformis muscle in relationship to the cause of sciatic pain. It was felt that an explanation should be forthcoming for the selective effect on the sciatic nerve which is found so frequently, either in connection with the complaints which have been allocated to the sacro-iliac joint or in connection with those referred to the lower lumbar segment. The explanation which has been offered by Goldthwait and Osgood of the proximity of the lumbosacral cord to the sacro-iliac joint should not satisfy one, since mere contiguity and not contact may be spoken of. As Yeoman has pointed out, the pyriformis muscle and its fascia are interposed. Moreover, many patients have pain in the lower part of the back and even in the sacro-iliac joints without symptoms of a sciatic nature. It has already been intimated that the assumption of a sciatic neuritis will not answer. Something more is required to explain the considerable number of cases of long duration, extending even throughout years, in which there develop no clinical signs of organic disease of the nerve structure except pain. Little satisfaction is derived from speaking of this as referred or reflected pain, especially in view of the fact that there is a respectable number of cases which appear precisely similar but for the impairment of the achilles tendon reflex and without any other sign of organic damage to the nerve. This is not the picture of chronic peripheral neuritis, nor yet of radiculitis, as one is accustomed to find it under other circumstances. It was felt that another element must be found to explain this localizing effect on the sciatic nerve and more particularly on its component the common peroneal nerve. So commonly are the symptoms found within the distribution of the peroneal nerve that Cotugno himself remarked on the rarity with which the tibial nerve is involved. Therefore, the anatomic study was undertaken, the results of which may be but briefly summarized at this time. We felt justified in making the following conclusions:

1. The pyriformis muscle is constantly found to have a part of its origin from the capsule of the sacro-iliac joint, and it is the only muscle which bridges that joint.

2. The pyriformis muscle is in extremely close relationship with the sciatic nerve. In 10 per cent or more of cadavers the nerve is found to pass through its substance. Between the pyriformis muscle

2. Freiberg, A. H., and Vinke, T. H.: Sciatica and the Sacro-Iliac Joint, J. Bone & Joint Surg. **16**:126-136 (Jan.) 1934.

3. Yeoman, W.: Relation of Arthritis of Sacro-Iliac Joint to Sciatica, Lancet **2**:1119, 1928.

and the trunk of the sciatic nerve there is a rich vascular plexus coming from the inferior gluteal vessels; pressure here would call forth a passive hyperemia of the sheath of the trunk of the sciatic nerve.

3. Experiment on cadavers showed that by the Lasègue maneuver the pyriformis muscle is put on the stretch after only a few degrees of straight leg raising through the medium of the biceps femoris muscle and its connection with the great sciatic ligament from which the pyriformis muscle derives a part of its origin uniformly. Since part of the pyriformis muscle is constantly derived also from the capsular ligament of the sacro-iliac joint, it may be expected to react by spasm as the result of disease in this joint. It may conceivably be involved by direct extension of disease from the sacro-iliac joint, or independently.

It is important to bear in mind the anatomic relationships shown in the illustrations in connection with the effects of certain surgical procedures which will be referred to presently. The following anatomic facts seem to be entitled to special emphasis. Since either the trunk of the whole sciatic nerve or, more often, the peroneal component of it perforates the pyriformis muscle in a considerable proportion of persons, the possibility of direct involvement of nerve must be granted in case of disease or spasm of the muscle. Even when this is not the case, the nerve lies directly against the bone of the great sciatic notch and may, conceivably, be compressed on it by the pyriformis muscle, inflamed or spastic, as the case may be. The gluteus maximus muscle, one of the most powerful and bulky muscles of the body, overlies the pyriformis muscle directly. That considerable part of it which does so inserts chiefly into the fascia lata, on the state of tension of which its own tonicity is conditioned. It follows that with marked impairment of this tonicity there will result a definite diminution of tension over the pyriformis muscle on the one hand and a similar hypotensive effect on the lower portion of the lumbodorsal fascia on the other hand. While the function of the gluteus maximus muscle as a part of the tensor mechanism of the thigh has been recognized by anatomists, it is likely that the magnitude of the rôle that it thus plays has hitherto not been realized. It may be observed here that in the severe flexion contractures of the hip which one often sees as the result of poliomyelitis sciatic pain is not present, although abductor contracture of the iliotibial band is most often associated with it. Here, however, paralysis of the gluteus maximus muscle is commonly dealt with, and it is therefore flaccid. Even should one grant such a possibility, therefore, one cannot expect a compressive effect on the pyriformis muscle under these circumstances.

PRACTICAL DEDUCTIONS

The effect of our anatomic study was to make us believe that the relationship of the pyriformis muscle to the sciatic nerve is of practical importance. In concluding the original paper, surgical attack on the pyriformis muscle was merely alluded to. By the time of its appearance in print this had already been carried out in several cases which were considered appropriate. It is not the present purpose to dis-

Fig. 1.—Drawing showing the portion of the fascial origin of the pyriformis muscle (*A*) which springs from the capsule of the sacro-iliac joint (*B*). This slip of origin is seen to the right of *B*. *C* indicates the obturator internus muscle. (Modified from Toldt: J. Bone & Joint Surg. **16**:126-136 [Jan.] 1934. This illustration is reproduced by permission of the publishers.)

cuss the general diagnosis of sciatic pain. On the contrary, it is proposed to assume the exclusion of all cases of pain due to disease of the central nervous system, those of pain due to neoplastic or inflammatory disease of viscera and those in which the basis is a frankly recognizable disease of the spinal radicles or of the sciatic nerve and

its components. It has been known for some years, particularly to the orthopedic surgeon, that many patients with sciatic pain which was felt to be attributable to a lesion of the sacro-iliac joint have responded remarkably well to traction applied to the lower extremity in the position of moderate abduction and flexion of the hip. When this happens, relief is likely to be experienced within forty-eight hours. In a certain number of cases, and especially in those in which the

Fig. 2.—Drawing showing the sacrotuberous ligament (*B*) and above it the fascial origin of the pyriformis muscle (*A*) springing from it. At *C* is shown the continuity of fibers from the tendon of the biceps with those of the sacrotuberous ligament. When the biceps is put on the stretch, as in the straight leg-raising or the Lasègue test, the pyriformis muscle is also made taut. (Modified by Toldt: J. Bone & Joint Surg. **16**:126-136 [Jan.] 1934. This illustration is reproduced by permission of the publishers.)

pain is not of very long duration, the relief is continuous, particularly if mechanical support of the lower part of the back is provided. In a few instances, however, especially in those in which the condition

is of long duration, pain recurs when traction is discontinued and activity is resumed. In such instances further help is demanded. Nerve stretching has been done in the past with little satisfaction, according to most reporters, and various methods of injection have been employed without conspicuous success. Were this otherwise, this whole discussion would be superfluous. So, too, has passed the vogue for forcible manipulation, the issue of which was at times very unhappy. There followed a period of operative intervention, ushered in by Smith-Petersen with fusion of the sacro-iliac joint. Other operations were also employed, such as fusion of the lumbosacral articulation and attack on the articular process of the fifth lumbar vertebra, according to

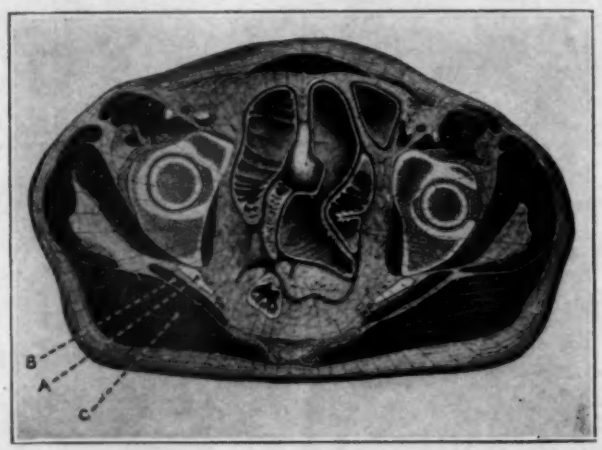

Fig. 3.—A cross-section just above the trochanter major. Here the trunk of the sciatic nerve lies directly on the iliac bone at the notch (*A*); the pyriformis muscle (*B*) is in close contact with it posteriorly and separated from it only by its thin, enveloping layer of fascia. In immediate contact with the pyriformis muscle posteriorly is the large mass of the gluteus maximus muscle (*C*), which inserts in considerable part into the fascia lata. According to Braus, the greatest part of the fibers of the gluteus maximus muscle arise from the sacrotuberous ligament; some of them arise from the lumbodorsal fascia. Through these, the action of the muscle is transmitted to the spinous processes of the lowermost lumbar vertebrae. (From Eycleshymer and Shoemaker: Cross Section Anatomy, section 40. Published by permission of D. Appleton-Century Company, Inc., New York.)

whether the sponsors attributed the symptom to lesions or to structural abnormalities in that situation. For the most part the operations involved have been of no mean gravity to the patient and have required long periods of convalescence, nor have they been without difficulty to the operator. There is no question but that fusion of the sacro-iliac joint was done in many cases with definite success; in not a few the

operation failed of such reward. The cause for failure, of course, may have lain in faulty diagnosis.

The first case in which an operative attack was made on the pyriformis muscle for sciatic pain was that of a woman 30 years of age. Partial thyroidectomy had been done about ten months before, because of hyperthyroidism of atypical character. Traction had furnished only temporary help. Fusion of both sacro-iliac joints had been done by the Campbell, or extra-articular, method. Relief following these operations did not endure. Seven months after the second of the fusion operations had been done, the patient returned, pleading for relief. Careful study failed to show any cause in the nervous system or, indeed, elsewhere. The Lasègue sign was positive, and there was tenderness over the sciatic notch of both sides. Section of the pyriformis muscle was done on one side, and the patient was sent home in a few days, free from pain on this side and with instruction

Fig. 4.—A cross-section made just below the tip of the trochanter major. Here the obturator internus and the gemelli muscles (*B*) are interposed between sciatic nerve (*A*) and bone. (From Eycleshymer and Shoemaker: Cross Section Anatomy, section 41. Published by permission of D. Appleton-Century Company, Inc., New York.)

to return should she desire the operation done on the other side. She returned in less than one month, asking for the second operation; this also was successful. A letter was received from her two years afterward expressing her gratitude for the continuance of complete comfort; she had recently been married and inquired about the risk of maternity.

OTHER EXPLANATIONS

Since the appearance in January 1934 of the two communications on this subject with which I have been associated, two contributions of significance have been made which concern themselves with operative procedures. In October 1934 Heyman [4] described two cases in which

4. Heyman, C. H.: Thoughts on Relief of Sciatic Pain, J. Bone & Joint Surg. **16**:889-894, 1934.

immediate relief was given and maintained by subperiosteal stripping of the gluteus maximus muscle and ligaments from the posterosuperior spine of the ilium. In his second case both forcible manipulation and fusion of the sacro-iliac joint had been done without abiding relief. The Lasègue sign was positive in both cases. He expressed the belief that his experience eliminates the pyriformis muscle from the discussion in these two instances.

In May 1935 Ober [5] published a paper on back strain and sciatica in which the ground is taken that the iliotibial band is an exceedingly important factor in the occurrence of lame back, with or without associated sciatica. He described the condition of abduction contracture of the hip joint which he found in such cases, as well as the method of recognizing it clinically. An account is given of a number of cases in which prompt and satisfactory relief was given by incision of the iliotibial band below the anterior superior iliac portion of the spine. There is no disposition whatever to question the claim of relief by this means; indeed, it has been possible for me to substantiate this by several such operations, done consequent on this publication. However, the aid which is brought to a patient with sciatic pain by this means brings with it questions the answers of which it would seem important to find. Ober's explanation is:

> First, that the shortness of the iliotibial band and the contracture of the fascia lata cause a squeezing effect on the sciatic nerve where it passes over the acetabulum. Second, an explanation which seems more reasonable, that the mechanical pull on the contracted bands or band is producing a mechanical strain of the sacro-iliac or lumbosacral articulation.

However, both these explanations seem to me inadequate: the first, because the relationship to the acetabulum is not close enough; the second, because it has hitherto not been clear why a lesion of the sacro-iliac joint should produce sciatic pain. In the case of a structurally normal sacrolumbar joint it is still less so. Examination of persons without either sciatic pain or pain in the back has shown in several instances the existence of well marked abduction contracture of the hip. On the other hand, in a number of cases of long-continued sciatic pain which were otherwise precisely similar, so far as we could tell, there was ascertainable no abductor contracture of the hip whatever. One is, furthermore, entitled to ask: Why are some abductor contractures of the hip productive of lame back without sciatica and why some others of sciatica without lame back? The obvious answer would be that there are other accompanying conditions, either in the sacro-iliac or in the lumbosacral joint, which determine such localization of

5. Ober, F. R.: Back Strain and Sciatica, J. A. M. A. **104**:1580-1583 (May 4) 1935.

symptoms. It seems much more rational to say that when incision of a contractured iliotibial band brings relief from sciatic pain it is because relaxation of the general tension of the fascial tube of the thigh and more especially of the fibers of the gluteus maximus muscle brings release of pressure on a pyriformis muscle and sciatic nerve which are under abnormal conditions to begin with.

A man approaching 50 years of age, who was operated on only recently, presented severe sciatic pain, which had recurred after being relieved by long-continued fixation in a plaster cast and rest in bed. Evident structural damage to the sacro-iliac joint was observed in the roentgenogram; the lesion, while not extensive, appeared to be destructive, and there was a positive cutaneous reaction to tuberculin in a dilution of 1:10,000. The achilles tendon reflex was markedly impaired, but no sensory or other reflex disturbance could be found. The Lasègue sign was positive, and there was marked and constant tenderness at the sciatic notch and over the mesial part of the pyriformis muscle. The Ober sign of abduction contracture of the hip was definitely positive on both sides. Accordingly, incision of the iliotibial band was done on the side of the sciatic pain, local anesthesia being used. Prompt subsidence of the pain resulted, and the condition has remained entirely satisfactory thus far.

In contrast to this case, I wish to cite another, that of a traveling salesman approaching 40 years of age. He was well except that for two years he had been suffering from pain in the lower part of the back, radiating down the back of the left thigh and latterly extending to the foot. The pain had been excruciating and interfered greatly with sleep. He had worn various supports and had tried different kinds of treatment without result. General examination gave essentially negative results. The Lasègue sign was positive on the left, and there was marked tenderness of the lower part of the left sacro-iliac joint, particularly at the sciatic notch. The achilles tendon reflex was exceedingly weak. Vibration sense was normal, and so were the results of all tests for cutaneous sensibility. The Ober test for abduction contracture was, however, indubitably negative on both sides. On July 22, 1935, the pyriformis muscle was exposed and incised between clamps. About ½ inch (1.3 cm.) of it was excised, and the ends were ligated with catgut. The trunk of the sciatic nerve was exposed; it appeared to pass anterior to the whole of the belly of the pyriformis muscle, so far as could be seen, but the critical portion of the muscle could not well be disclosed in this wound. The man was at once relieved and has remained so, being last seen on Dec. 21, 1935.

In both of the cases just reported the patient was subjected to thorough general, serologic, visceral and neurologic study before we arrived at any conclusions. I have omitted details to avoid prolixity.

These two cases would appear to illustrate two interesting things: in the first instance, that sciatic pain which I, at least, felt should be attributed to the pyriformis muscle could be relieved by cutting the iliotibial band when in contracture; in the second, that sciatic pain similarly charged to the pyriformis muscle and entirely relieved by its section could exist in the absence of the Ober sign of abduction contracture. It would therefore appear possible to have abductor contracture without either pain in the back or sciatic pain, just as it appears

possible to have sciatic pain of the kind being considered in the absence of the Ober sign. On both anatomic and clinical grounds, the conclusion which I draw is that the operations of Heyman and Ober alike owe what effectiveness they have to their action through the gluteus maximus muscle, so far as sciatic pain is concerned, but that it is through the medium of the pyriformis muscle after all. Because of its more superficial location, the procedure of Ober on the iliotibial band is somewhat simpler than myotomy of the pyriformis muscle. Nevertheless, the operation on the pyriformis muscle, also, is easily done with local anesthesia. With us, the iliotibial band has been cut for sciatic pain with the feeling that the operation on the pyriformis muscle was still available in case of need. But it does seem illogical to divide the iliotibial band when there is no evidence of its contracture, and sufficient warrant appears for believing that this happens in cases of sciatic pain which in all other respects belong in the same grouping. In a personal communication, Dr. Leo Mayer, of New York, has described a case in which sciatic pain was relieved by incision of the iliotibial band but recurred after six weeks. The question thus arises whether in the presence of such contracture not only the iliotibial band but also the pyriformis muscle should be incised.

I shall not fail to emphasize my realization of the fact that in both of these operations one is most often dealing with what is merely a symptomatic release. Unless one credits the muscle or the fascia, as the case may be, with being the seat of the primary lesion this will be true. While this may be the case, it is in my opinion most often not so; in the contrary event, it will be difficult to determine this definitely. Thus far, the proposal to relieve sciatic pain by operation on the pyriformis muscle has been made only for patients who have their symptoms entirely within the field of sciatic distribution. Perhaps in the future it may be found undesirable to restrict its use thus. I must not omit to state, however, that whereas cases are observed in which the clinical study points to the pyriformis muscle as the direct cause of pain, at the same time there is reason to believe that this is incidental to disease in the sacro-iliac joint and that the sacrolumbar and even the lumbar segment of the spine may also be implicated. It would obviously constitute an inexcusable error to look on an operation on the muscle or fascia to relieve pain as fulfilling one's task when one's responsibility demands that this be followed by the mechanical and constitutional measures which are calculated to control the fundamental condition which has occasioned the pain. I fear that I have already observed evidence of such a mistaken attitude toward these operations. Unless such precaution is heeded one may expect recrudescences, which are avoidable.

In Lasègue's [6] monograph there is a statement which has intrigued me. He said:

> My conviction is that the study of the diseases of the brachial plexus should parallel those of the sciatic plexus; that their differences provide as much information as their resemblances. It is regrettable that Cotugno, having had the primary idea, should have abandoned it hastily, instead of pursuing it.

This statement came back to me recently when my attention was attracted to an article by Ochsner, Gage and DeBakey.[7] There is here described what the authors term "a clinical entity, the symptoms of which are identical with those of cervical rib. . . . The treatment consists of resection of a portion of the scalenus anticus muscle." It does not seem opportune to enter further into the discussion of this phase now. Suffice it to say that while the anatomic conditions are by no means the same, neither may they be said to be entirely heterologous nor the analogy altogether fantastic.

CONCLUSIONS

Even though I deem it scarcely necessary at this juncture to insist again on the primary necessity of making the general examination with exacting care and thoroughness in order that a correct diagnostic conclusion may be reached before advocating such operative measures as have been set forth, I shall not forbear from so doing. This having been complied with, I still plead for a wise conservatism. I am much too cognizant that in the past many patients belonging in the class under discussion have been brought to cure without operation whether by means of traction and mechanical support or by means of epidural or paravertebral injections. This is not to say, on the other hand, that it is justifiable to prolong unduly the period of distress or invalidism in order to avoid an operation which in skilled hands is free from danger as well as from later undesirable consequences. No patient who has thus far been operated on has shown any loss of function. There remain to be stated the conditions under which it has thus far been felt justifiable to do section of the pyriformis muscle, that of the iliotibial band or the two combined, even though I have not yet advocated the combined procedure in any case. Once the diagnosis appears sufficiently clear, the primary considerations involve the questions of chronicity, of severity of pain and of recurrence after relief has been secured by other means. The determining criteria which give promise for the favorable outcome of the operation are: a positive Lasègue sign, tender-

6. Lasègue, C.: Consideration sur la sciatique, Arch. gén. de méd. **2**:558, 1864.

7. Ochsner, Alton; Gage, Mims, and DeBakey, Michael: Scalenus Anticus Syndrome (Naffziger), Am. J. Surg. **28**:669-696, 1935.

ness at the sciatic notch and definite relief from traction properly applied. I feel that it is too early to say that there are precise data on which to base a preference for section of the pyriformis muscle; my reasons will be apparent from what I have already said. Neither am I ready to say that fusion operations are to be entirely abandoned. I do say, however, that by means of these myofascial operations the field of fusion has been greatly narrowed, perhaps to the degree of reserving it for certain cases of destructive disease.

In conclusion, it seems entirely justifiable to say that by means of these relatively simple and safe procedures one is enabled to offer a new hope to a group of patients to whom, until now, professional efforts had seemed well nigh fruitless and illusory. I am convinced that there are more of them than many have believed. It is no small thing for them or for the surgeon to be able to supplant their despair by surcease of suffering.

PARA-AMINOBENZENESULFONAMIDE AND ITS DERIVATIVES

CLINICAL OBSERVATIONS ON THEIR USE IN THE TREATMENT OF INFECTIONS DUE TO BETA HEMOLYTIC STREPTOCOCCI

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AND

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During the past three years an ever increasing volume of favorable reports [1] have emanated from Europe concerning the use of para-aminobenzenesulfonamide and its derivatives in the treatment of infections due to beta hemolytic streptococci. During the past few months we have had the opportunity of employing these new specific chemotherapeutic agents in the treatment of experimental and clinical infec-

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1. (*a*) Foerster: Zentralbl. f. Haut- u. Geschlechtskr. **45**:549, 1933. (*b*) Grütz, O.: ibid. **49**:300, 1934; Med. Klin. **30**:52, 1934. (*c*) Veil, W.: Therap. d. Gegenw. **75**:212, 1934. (*d*) Gmelin, L.: München. med. Wchnschr. **82**:221, 1935. (*e*) Domagk, G.: Deutsche med. Wchnschr. **61**:250, 1935; Angew. chem. **48**:657, 1935. (*f*) Klee, P., and Romer, H.: Deutsche med. Wchnschr. **61**:253, 1935. (*g*) Schreus, H.: ibid. **61**:255, 1935. (*h*) Anselm, E.: ibid. **61**:264, 1935. (*i*) Gantenberg, R.: ibid. **61**:284, 1935. (*j*) Gantenberg, R., and Thimme, B.: Med. Welt **9**:1009, 1935. (*k*) Imhaeuser, K.: Med. Klin. **31**:282, 1935. (*l*) Schranz, H.: München. med. Wchnschr. **82**:419, 1935. (*m*) Levaditi, C., and Vaisman, A.: Compt. rend. Acad. d. sc. **200**:1694, 1935; Compt. rend. Soc. de biol. **119**:946, 1935. (*n*) Nitti, F., and Bovet, D.: ibid. **119**:1277, 1935. (*o*) Recknagel, K.: München. med. Wchnschr. **82**:704, 1935. (*p*) Bingold, K.: ibid. **82**: 871, 1935. (*q*) Einhaeuser: ibid. **82**:1463, 1935; Deutsche med. Wchnschr. **61**:1263, 1935. (*r*) Fuge, K.: ibid. **61**:1263, 1935. (*s*) Roth, A.: ibid. **61**:1734, 1935. (*t*) Puschel, E.: Fortschr. d. Therap. **11**:96, 1935. (*u*) Temming, H.: Kinderärztl. Praxis **9**:400, 1935. (*v*) Fasal: Med. Klin. **31**:898, 1935. (*w*) Tréfouël, J.; Nitti, F., and Bovet, D.: Compt. rend. Soc. de biol. **120**:756, 1935. (*x*) Riecke, H.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **38**:175, 1935. (*y*) Tixier, L., and Eck, M.: Bull. Soc. de pédiat. de Paris **33**:493, 1935. (*z*) Lampert, J.: Zentralbl. f. Chir. **62**:2947, 1935. (*a'*) Scherber, G.: Wien. med. Wchnschr. **85**:284, 346 and 783, 1935; **86**:22, 1936. (*b'*) Bloch-Michel, H.; Conte, M., and

(Footnote continued on next page)

tions produced by beta hemolytic streptococci. We have discussed our preliminary observations in a previous report.[2] In this communication we shall describe briefly the action of the compounds which we have tested and detail our experiences in the clinical use of para-aminobenzenesulfonamide and its derivatives in the treatment of human beings with infections due to hemolytic streptococci.

EXPERIMENTAL OBSERVATIONS

In the course of our investigations we have used two samples of para-aminobenzenesulfonamide, one supplied to us by E. I. DuPont de Nemours and Company and the other by the Winthrop Chemical Company. Two derivatives of this substance have also been studied. One of these, the hydrochloride of 4′-sulfamido-2, 4-diamino-azo-benzene was sent to us in tablet form, labeled "prontosil tablets," while the second, the disodium salt of 4′-sulfamidophenyl-2-azo-7-acetyl-amino-1-hydroxynaphthalene-3, 6-disulfonic acid, was supplied to us as a red liquid, labeled "prontosil, 2.5 per cent solution." Tablets containing 0.3 Gm. of para-aminobenzenesulfonamide in a starch base, labeled "prontylin," were also used in our experimental and clinical investigations. All three of the preparations bearing trade-marked names were supplied by the Winthrop Chemical Company.

Our preliminary observations confirmed the report of Colebrook and Kenny [1f′] that prontosil solution had little if any effect on hemolytic streptococci in vitro. However, we soon observed that a concentration of 1 : 10,000 of para-aminobenzenesulfonamide had a marked bacterio-

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Durel, P.: Presse méd. **44**:1583, 1935. (*c′*) Buttle, G.; Gray, W., and Stephenson D.: Lancet **1**:1286, 1936. (*d′*) Caussé, Loiseau, and Gisselbrecht: Ann. d'oto-laryng., February 1936, p. 194. (*e′*) Colebrook, L.; Buttle, G., and O'Meara, R.: Lancet **2**:1323, 1936. (*f′*) Colebrook, L., and Kenny, M.: ibid. **1**:1279, 1936; (*g′*) **2**:1319, 1936. (*h′*) Doerfler, H.: München. med. Wchnschr. **83**:1913, 1936. (*i′*) Domagk, G.: Klin. Wchnschr. **15**:1585, 1936. (*j′*) Férey, D.: Bull. méd., Paris **50**:230, 1936. (*k′*) Floch, H.: Bull. Soc. path. exot. **29**:165, 1936. (*l′*) Gley, P., and Girard, A.: Presse méd. **44**:1775, 1936. (*m′*) Goissedet, P.; Despois, R.; Gailliot, P., and Mayer, R.: Compt. rend. Soc. de biol. **121**:1082, 1936. (*n′*) Hörlein, H.: Proc. Roy. Soc. Med. **29**:313, 1936. (*o′*) Kramer, W.: München. med. Wchnschr. **83**:608, 1936. (*p′*) Lemierre, A.; LaPorte, A.; Laudat, M., and Daum: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:535, 1936. (*q′*) Levaditi, C., and Vaisman, A.: Compt. rend. Soc. de biol. **121**:803, 1936. (*r′*) Ley, L.: München. med. Wchnschr. **83**:1092, 1936. (*s′*) Meyer-Heine, A., and Huguenin, P.: Presse méd. **44**:454, 1936. (*t′*) Sigel, O.: Fortschr. d. Therap. **12**:229, 1936. (*u′*) Vermelin and Hartmann: Bull. Soc. d'obst. et de gynéc. **25**:158, 1936.

2. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection; a Preliminary Report, J. A. M. A. **108**:32 (Jan. 2) 1937.

static action on beta hemolytic streptococci when tested in vitro in the presence of beef infusion broth or 50 per cent normal horse serum broth. This observation has been independently arrived at by Colebrook and his co-workers.[1e']

It had been shown by Domagk and Colebrook and Kenny and others [3] that while prontosil solution was inactive in vitro, it had a very active chemotherapeutic effect in vivo. In our previous report we postulated the hypothesis that a reduction of the chemical substance in prontosil solution occurred in vivo in the presence of infection and that the reduced form represented para-aminobenzenesulfonamide. We have been able to repeat this observation in vitro by demonstrating the bacteriostatic action of prontosil solution that has been reduced to the active form by cysteine hydrochloride.[4]

The importance of the rôle of reduction in the activation of prontosil solution has been recently and independently pointed out by Colebrook and his co-workers.[1e']

In our previous communication [2] we reported that we had been able to confirm in part the reports of European investigators [5] regarding the efficacy of these chemotherapeutic agents in the treatment of infections produced experimentally in mice with beta hemolytic streptococci. Our immediate results compared favorably with their results. However, we have now to report that mice have died of streptococcic infection as late as seventy-four days after the infection or sixty days after treatment with prontosil solution had been discontinued. During the interval the mice had apparently enjoyed good health, but still they succumbed to the original infection after this relatively long period. These late deaths cannot be explained at the present time. It should be noted, however, that the strains we employed in our experimental observations had a high virulence for mice, a hundred millionth of a cubic centimeter of the twelve hour blood broth culture containing from two to five minimal lethal doses, so that if one streptococcus survived it would presumably be capable of multiplying and eventually killing a mouse.

Experimental observations on the mode of action of these compounds lead us to believe that they act by inhibiting the growth of beta hemolytic streptococci and that they injure these organisms in such a way as to permit them to be phagocytosed by the white blood cells. Recent observations on the exudate in experimental streptococcic peritonitis in mice have shown that inhibition of growth and phagocy-

3. Domagk.[1e] Colebrook, Buttle and O'Meara.[1e'] Colebrook and Kenny.[1f'] Colebrook and Kenny.[1g']

4. Bliss, E., and Long, P.: Bull. Johns Hopkins Hosp., to be published.

5. Domagk.[1e] Levaditi and Vaisman.[1m] Nitti and Bovet.[1n] Tréfouël, Nitti and Bovet.[1w] Colebrook and Kenny.[1f']

tosis of the organisms occur about six to eight hours after the injection of the chemotherapeutic agent into the animal body. This lag in action suggests the possibility of a change in the chemical substances after their introduction into the animal organism.

CLINICAL OBSERVATIONS

We have used the following preparations in the treatment of human beings with infections due to beta hemolytic streptococci:

1. A 2.5 per cent solution of the disodium salt of 4′-sulfamidophenyl-2-azo-7-acetylamino-1-hydroxynapththalene-3, 6-disulfonic acid, labeled "prontosil, 2.5 per cent solution." This preparation was always used parenterally.

2. Tablets containing 0.3 Gm. of the hydrochloride of 4′-sulfamido-2, 4-diamino-benzene, labeled "prontosil tablets." (This compound is no longer available.)

3. Tablets containing 0.3 Gm. of para-aminobenzenesulfonamide, labeled "prontylin."

4. Two samples of chemically pure para-aminobenzenesulfonamide.

With these preparations, singly and in combination, we have treated seventy persons ill with infections due to beta hemolytic streptococci. The types of disease treated and the results of treatment are given in the accompanying table.

Types of Infections Produced by Beta Hemolytic Streptococci Treated with Para-Aminobenzenesulfonamide and Its Derivatives

Type of Infection	No. of Patients	Recovered	Died
Erysipelas and cellulitis	19	19	0
Septicemia	3	2	1
Puerperal sepsis	2	2	0
Traumatic orbital cellulitis	3	3	0
Osteomyelitis	2	2	0
Cystitis	3	3	0
Peritonitis	1	0	1
Tonsillitis	14	14	0
Peritonsillar infections	5	5	0
Scarlet fever	8	8	0
Ludwig's angina	2	0	2
Otitis media	9	9	0

The clinical results obtained in the treatment of human beings with infections produced by beta hemolytic streptococci have been striking. While our series of patients who have received treatment is not large enough for accurate statistical analysis based on mortality figures, in practically every instance marked clinical improvement in the patient's condition occurred promptly after the administration of para-aminobenzenesulfonamide or its derivatives.

In the group of seventy patients in whom these preparations have been used as therapeutic agents there have been four deaths. The first

death, that of a 57 year old Negro, occurred seven hours after treatment was commenced for a hemolytic streptococcic septicemia of several days' duration. The man was considered to be moribund when treatment was instituted. The two patients ill with Ludwig's angina died twenty hours and about thirty-five hours, respectively, after treatment was commenced. We do not believe that any of these cases represent a failure of the therapeutic agents employed. However, the fourth death in our series occurred in a 4 month old infant ill with peritonitis due to beta hemolytic streptococci who had received adequate therapy for twelve days before death suddenly occurred. This we consider to represent a failure of the specific therapy.

Our observations, both experimental and clinical, on the treatment of streptococcic infections lead us to believe that about forty-eight hours is required before maximum therapeutic effects can be obtained with para-aminobenzenesulfonamide or its derivatives. Because of this time factor we feel that if an infection is considered to be due to hemolytic streptococci treatment should be instituted immediately. Also striking results should not be expected when patients with far advanced infections or those who are moribund are treated.

As a result of our experiences in treating these seventy patients ill with hemolytic streptococcic infections we have been able to formulate certain rules for estimating the amount of drug needed in the treatment of acute infections due to streptococci of this type.

When prontosil, 2.5 per cent solution, is used, the total amount required during the first twenty-four hours of treatment is calculated on the basis of 1 cc. for each pound (0.5 Kg.) of body weight up to 120 pounds (54.4 Kg.). For patients over this weight the first day's dose is 120 cc. The total daily amount is divided into six parts, and a dose is given every four hours by a subcutaneous injection. An example is that of a patient weighing 120 pounds who would receive 120 cc. of prontosil solution during the first twenty-four hours of treatment in six subcutaneous injections of 20 cc. each. Prontosil, 2.5 per cent solution, is rapidly absorbed and should not be administered by the intravenous or intrathecal route.

Prontylin tablets are to be used only for oral administration. The total dose for the first twenty-four hours is calculated on the basis of 3 tablets (1 Gm.) for each 20 pounds (9.1 Kg.) of body weight up to 100 pounds (45.4 Kg.). In the treatment of acute infections we believe that 5 Gm. of this substance represents the maximum daily dose in adults which may be used with safety. This total amount is divided into four doses given at intervals of six hours. Thus, for a patient weighing 100 pounds the total amount required for the first day would be 16 tablets, or 4 tablets every six hours.

Para-aminobenzenesulfonamide is not generally available at the present time, nor is it yet entirely satisfactory for use, because of certain difficulties in its administration. However, during the past few months, in cases of severe infections we have been instituting treatment by giving a hypodermoclysis of para-aminobenzenesulfonamide dissolved in sterile physiologic solution of sodium chloride. This chemical is soluble up to roughly 0.8 per cent in hot physiologic solution of sodium chloride. In the preparation of this substance for clinical use, it is our practice to dissolve 0.8 Gm. in 100 cc. of physiologic solution of sodium chloride which has been brought to the boiling point and then cooled to 90 C.

The solution is then cooled to 37 C. and is given by hypodermoclysis into loose subcutaneous tissue. The amount of chemical given by this method is gaged by the weight of the patient. We use 0.8 Gm. in 100 cc. of physiologic solution of sodium chloride for patients weighing up to 40 pounds (18 Kg.). For those weighing between 40 and 80 pounds (18 and 36 Kg.) the dose is 1.6 Gm. of the chemical in 200 cc. of physiologic solution of sodium chloride. Patients weighing between 80 and 120 pounds (36 and 54.5 Kg.) receive 2.4 Gm. dissolved in 300 cc. of physiologic solution of sodium chloride, while for patients weighing over 120 pounds the dose is 3.2 Gm. of para-aminobenzenesulfonamide dissolved in 400 cc. of physiologic solution of sodium chloride. These solutions are administered soon after preparation because of the tendency of the chemical to crystallize out of solution on standing at temperatures lower than 37 C.

An 0.8 per cent solution of para-aminobenzenesulfonamide in physiologic solution of sodium chloride may also be used intrathecally in the treatment of streptococcic meningitis.[6] In general, it has been the experience of those who have used para-aminobenzenesulfonamide in this way that little cellular reaction to the chemical has been observed and no toxic manifestations. The general practice in administering para-aminobenzenesulfonamide intrathecally should closely follow that recommended for the use of antimeningococcus serum in meningococcic meningitis, namely, that rather complete spinal drainage by lumbar puncture should be instituted and then from 15 to 25 cc. of a warm, freshly prepared 0.8 per cent solution of para-aminobenzenesulfonamide should be permitted to flow in by gravity. The solution should never be injected under pressure.

As the result of our observations we believe that the following suggestions represent effective amounts of para-aminobenzenesulfonamide or its derivatives during the first twenty-four hours of treatment in streptococcic infections of varying degrees of severity.

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6. Schwentker, Francis F.: Personal communication to the authors. Edwards, Lydia: Personal communication to the authors.

In severe infections in which the immediate prognosis is grave, either prontosil, 2.5 per cent solution, or para-aminobenzenesulfonamide in an 0.8 per cent solution in physiologic solution of sodium chloride is given by the parenteral route in the recommended doses. In addition, prontylin tablets in one half of the estimated amount are given orally beginning about four hours after parenteral therapy has been instituted.

In moderately severe infections the patient is given either the estimated amount of prontosil, 2.5 per cent solution, parenterally or prontylin tablets orally during the first twenty-four hours of treatment. The drugs are not used in combination.

Mild or relatively chronic streptococcic infections can be controlled by the use of prontylin tablets alone, and as a rule in infections of little immediate severity from one half to two thirds of the estimated dose will be effective.

The question of the amount of the various chemicals needed after the first day of treatment has been completed is difficult to outline and should depend on the clinical condition of the patient. In cases of severe streptococcic disease it has been our practice to continue treatment on the original basis of the first day until a definite improvement in the condition of the patient has been noted. In the patient in whom a streptococcic septicemia is present we feel that at least two blood cultures should be negative for beta hemolytic streptococci before one starts to decrease the total daily amount of the chemical which is being employed.

In moderately severe streptococcic infections, especially those in which a visible lesion is present, such as erysipelas, peritonsillar abscess and scarlet fever, one must be governed in respect to further treatment entirely by the clinical appearance of the lesions and the general clinical condition of the patient. Rarely does one have to continue the chemical employed in full doses after the second twenty-four hours of treatment. At this point the amount of the drug may, if the clinical condition warrants, be cut by a quarter or a third and then gradually decreased over a period of a week. It should be borne in mind that if the drug is discontinued too soon a recurrence of the streptococcic lesion may occur.

When one is dealing with mild acute streptococcic infections, recovery after the administration of para-aminobenzenesulfonamide or its derivatives is generally so prompt that it seems safe to decrease rapidly the amount of the chemical administered. In mild chronic infections due to beta hemolytic streptococci, such as chronic impetigo and chronic otitis media, it is often necessary to administer the drug over a rather long period or until a definite clinical and bacteriologic cure is effected.

Even so, a recurrence of the infection may occur, but as control is again easily established with these chemicals, one should not be alarmed.

It may be asked, "How long can one administer para-aminobenzenesulfonamide to a patient without any danger?" On this point one can only say that a prolonged clinical experience with the drug will be necessary before the final answer is known. We have observed patients who have been given rather large amounts of para-aminobenzenesulfonamide (from 3 to 5 Gm. per day by mouth) over a period of several weeks without any ill effects.

When the question arises as to which preparation should be selected for use in the treatment of a given patient with hemolytic streptococcic infection, we can answer by saying that for patients who are able to swallow tablets para-aminobenzenesulfonamide given by mouth (in the form of prontylin tablets) is the most satisfactory from the point of view both of results obtained and of ease of administration. With patients who cannot swallow, or who are vomiting, parenteral medication is indicated, and either a solution of para-aminobenzenesulfonamide or the chemical which is marketed under the trade name of prontosil, 2.5 per cent solution, may be used. In this connection, it should be noted that 100 cc. of prontosil solution if completely broken down into the active form will deliver 0.73 Gm. of para-aminobenzenesulfonamide and that therefore one can in a given period reach a higher concentration of the effective principle with para-aminobenzenesulfonamide than with prontosil solution. On the other hand, owing to the difficulties attendant on the parenteral administration of para-aminobenzenesulfonamide, we believe that in most instances prontosil solution is the drug of choice.

It should also be noted that the daily and total dosage of these compounds which we have recommended is in excess of that advised by other observers.[7] We know, nevertheless, that these doses represent amounts that are rapidly effective. Undoubtedly as more information is gained concerning the use of these compounds in the treatment of streptococcic infections our proposals for dosage will be altered.

TOXICITY

When a new chemotherapeutic compound is being tested for clinical use it is of the utmost importance to observe whether or not the drug itself has any toxic effects on the animal body. In the case of para-aminobenzenesulfonamide and its derivatives, we may say that there is little evidence that these compounds are appreciably toxic for human beings, at least as far as their immediate effects are concerned. The evidences of toxicity which have been observed are the following:

7. Colebrook and Kenny.[1f] Colebrook and Kenny.[1g]

A few patients have complained of nausea, ringing in the ears or slight dizziness shortly after the ingestion of the first oral dose of tablets containing para-aminobenzenesulfonamide. These symptoms pass off rapidly as a rule and have not, so far, contraindicated the use of the compound.

If prontosil, 2.5 per cent solution, is given in a single dose of 100 cc. subcutaneously or in repeated smaller doses, fever may result. Bennett [8] has noted that normal human beings who receive a single large dose (100 cc.) of prontosil solution by the subcutaneous route exhibit fever within twenty-four hours. We have also noted that the rather prolonged administration of large doses (5 Gm. per day) of tablets containing para-aminobenzenesulfonamide will also produce fever which disappears within twenty-four hours after the drug is discontinued. This toxic manifestation of these compounds is of importance in severe cases of streptococcic infection in which sometimes one's clinical judgment must be carefully exercised in order to differentiate between fever produced by the infection and fever produced by the chemical.

Four patients have exhibited slight cyanosis coupled with rapid breathing while under treatment. These symptoms are the result of acidosis. Jaundice developed in one patient while he was under treatment, and recovery occurred promptly after para-aminobenzenesulfonamide was discontinued. This patient has subsequently been given large doses of this drug without a recurrence of jaundice. The possibility of acute injury to the liver must be borne in mind. Colebrook and Kenny [11] reported that sulfhemoglobinemia developed in three patients while they were under treatment. He wondered whether the use of saline cathartics played a rôle in the production of the condition. None of our patients has received saline cathartics or laxatives, but sulfhemoglobinemia has developed in three.

None of the toxic manifestations which we have observed has been severe. The question of late delayed toxic effects from the use of these compounds can be answered only when our clinical experience with para-aminobenzenesulfonamide is more mature.

CONCLUSIONS

Para-aminobenzenesulfonamide and its derivatives have a specific chemotherapeutic effect in the treatment of infections produced by beta hemolytic streptococci. In our opinion, these chemicals have a low degree of toxicity. It seems logical to believe that the prompt recognition of the nature of hemolytic streptococcic infections plus the adequate administration of the specific chemotherapeutic agents will greatly lessen the dangers inherent in these types of infection.

8. Bennett, Stanley H.: Personal communication to the authors.

PERTHES' DISEASE

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Fifty-seven cases of Perthes' disease which were roentgenographed and studied in the Hospital for Joint Diseases between 1929 and 1936 formed the basis of this study. The aim of the analysis was to interpret the aberrations as noted on the roentgenograms in the light of current knowledge of pathologic processes in bone.

CLINICAL STATISTICS

The statistical data may be briefly summarized as follows:

1. Age at Which Symptoms Commenced.—The distribution of cases according to age was as follows: 3 years, three; 4 years, one; 5 years, nine; 6 years, eleven; 7 years, nine; 8 years, twelve; 9 years, five; 10 years, three; 11 years, none; 12 years, two; 13 years, one, and 14 years, one.

2. Hip Affected.—In twenty-eight cases, the right hip was affected; in twenty-six, the left, and in three, both hips.

3. Sex and Race.—The male patients numbered 45; the female patients, 12. All were white (from 15 to 20 per cent of the patients received in this hospital are colored).

4. Trauma.—This was present in twelve cases.

5. Interval Between First Trauma and First Visit to Institution.—This interval was one month in two cases; two months in one; three months in two; four months in two; one year in three; two years in one, and three years in one.

6. Pertinent Clinical Data.—Most of the patients complained of a limp or of pain in the affected hip region; some experienced pain in the ipsilateral knee; others were aware only of a dull ache about the hip; a few noted a slight shortening of the limb without accompanying pains.

7. Physical Findings.—The physical examinations demonstrated in some of the patients a fixed flexion adduction deformity of the femur in the involved hip joint. Limitation of internal and external rotation

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as well as of flexion, extension, abduction and adduction of the femur was encountered in many.

8. Measurements.—One of the procedures in the course of the study was to measure in fractions of an inch the distance (as revealed on the roentgen plate) from the summit of the outer portion of the femoral capital epiphysis to the directly opposed acetabulum. The measurements are given in table 1. Table 1 reveals that with the exception of two instances (excluding also three cases which were bilateral) the distance

TABLE 1.—*Distance (in Fractions of an Inch) from Summit of Outer Portion of Capital Epiphysis to Opposed Acetabulum*

Age, Years	Normal Hip	Abnormal Hip
3	6/16 (0.95 cm.)	6/16 (0.95 cm.)
4	3/16 (0.48 cm.)	6/16 (0.95 cm.)
5	4/16 to 6/16 (0.63 to 0.95 cm.)	4/16 to 7/16 (0.63 to 1.11 cm.)
6	2/16 to 6/16 (0.32 to 0.95 cm.)	4/16 to 6/16 (0.63 to 0.95 cm.)
7	3/16 to 5/16 (0.48 to 0.80 cm.)	4/16 to 7/16 (0.63 to 1.11 cm.)
8	4/16 (0.63 cm.)	4/16 (0.63 cm.)
9	4/16 to 6/16 (0.63 to 0.95 cm.)	4/16 to 8/16 (0.63 to 1.27 cm.)
10	4/16 to 6/16 (0.63 to 0.95 cm.)	2/16 to 4/16 (0.32 to 0.63 cm.)
11-14	2/16 to 6/16 (0.32 to 0.95 cm.)	2/16 to 6/16 (0.32 to 0.95 cm.)

TABLE 2.—*Height (in Fractions of Inch) of Outer Portion of Capital Epiphysis*

Age, Years	Normal Hip	Abnormal Hip
3- 6	6/16 to 10/16 (0.95 to 1.59 cm.)	2/16 to 8/16 (0.32 to 1.27 cm.)
7- 9	8/16 to 12/16 (1.27 to 1.90 cm.)	2/16 to 12/16 (0.32 to 1.90 cm.)
10-14	8/16 to 13/16 (0.27 to 2.06 cm.)	4/16 to 11/16 (0.63 to 1.74 cm.)

TABLE 3.—*Width (in Inches) of Upper Epiphysial Cartilage Plate*

Age, Years	Normal Hip	Abnormal Hip
3- 6	1 to 1 3/8 (2.54 to 3.48 cm.)	1 to 1 3/8 (2.54 to 3.48 cm.)
7- 9	1 2/8 to 1 7/8 (3.17 to 4.75 cm.)	1 1/16 to 2 (2.70 to 5.08 cm.)
10-14	1 to 1 7/8 (2.54 to 4.75 cm.)	1 to 2 1/4 (2.54 to 5.72 cm.)

was greater on the affected side. In two cases the joint space on the involved side was smaller.

Another procedure was to measure the height of the outer portion of the capital epiphysis. The involved side was smaller than the normal one during some phase of the disease. The exact data are given in table 2.

Still another procedure was to measure the width of the upper epiphysial cartilage plate, i. e., the distance from the superior to the inferior cortex of the femoral neck, just at their junction with the capital epiphysis. The findings are recorded in table 3.

The fourth item was the measurement of the length of the superior cortex of the femoral neck, i. e., the distance between the proximal surface of the greater trochanter and the upper femoral epiphysial cartilage plate. The data (table 4) show that extreme shortening of the femoral neck is not a frequent finding in the young.

The last procedure was the determination, by means of a protractor, of the angle formed at the junction of the femoral neck and the shaft. (A line was drawn bisecting the femoral neck; another line was drawn bisecting the upper portion of the femoral shaft.) The obtuse angle was measured where the two lines crossed. The data are given in table 5.

TABLE 4.—*Length (in Inches) of Superior Cortex of Femoral Neck*

Age, Years	Normal Hip	Abnormal Hip
3- 5	1/2 to 1 1/4 (1.27 to 3.18 cm.)	1/2 to 1 1/4 (1.27 to 3.18 cm.)
6	3/4 to 1 (1.91 to 2.54 cm.)	3/4 to 1 (1.91 to 2.54 cm.)
7	1/2 to 1 1/2 (1.27 to 3.81 cm.)	1/2 to 1 1/2 (1.27 to 3.81 cm.)
8	1/2 to 7/8 (1.27 to 2.22 cm.)	1/2 to 7/8 (1.27 to 2.22 cm.)
9	5/8 to 6/8 (1.60 to 1.90 cm.)	1/2 to 6/8 (1.27 to 1.90 cm.)
10	1 to 1 1/8 (2.54 to 2.86 cm.)	1 to 1 1/8 (2.54 to 2.86 cm.)
11-14	1 to 1 1/2 (2.54 to 3.81 cm.)	3/4 to 1 1/2 (1.91 to 2.54 cm.)

TABLE 5.—*Angle (in Degrees) Formed at Junction of Femoral Neck and Shaft*

Age, Years	Normal Hip	Abnormal Hip
3	150	150
4	135	135
5	135 to 145	135 to 145
6	140 to 150	140 to 150
7	140 to 145	140 to 145
8	135 to 145	135 to 145
9	130 to 140	125 to 135
10	130 to 140	125 to 135
11-14	140 to 150	130 to 150

PATHOLOGY

The second part of this paper relates to the pathologic processes that were probably responsible for the alterations in the configuration of the proximal portion of the femur as noted on the roentgenograms in our fifty-seven cases. This part of the paper will be divided into three sections. The first will deal with the changes in the upper epiphysis of the involved femur.

1. *Changes in the Upper Capital Epiphysis.*—Roentgenographic examination of normal hip joints of children shows that the bony portion of the capital epiphysis is by no means regularly outlined as a hemisphere or as an arc of a circle. We have frequently observed that the outline of the outer portion of the capital epiphysis is slightly taller

than the inner one (fig. 1 *A*). In several instances we have found also that the portion of the normal capital epiphysis situated close to the medial wall of the acetabulum appeared flattened as if compressed by the ligamentum teres.

With this in mind we observed that in the early stages of Perthes' disease the roentgenogram may exhibit only slight flattening of the

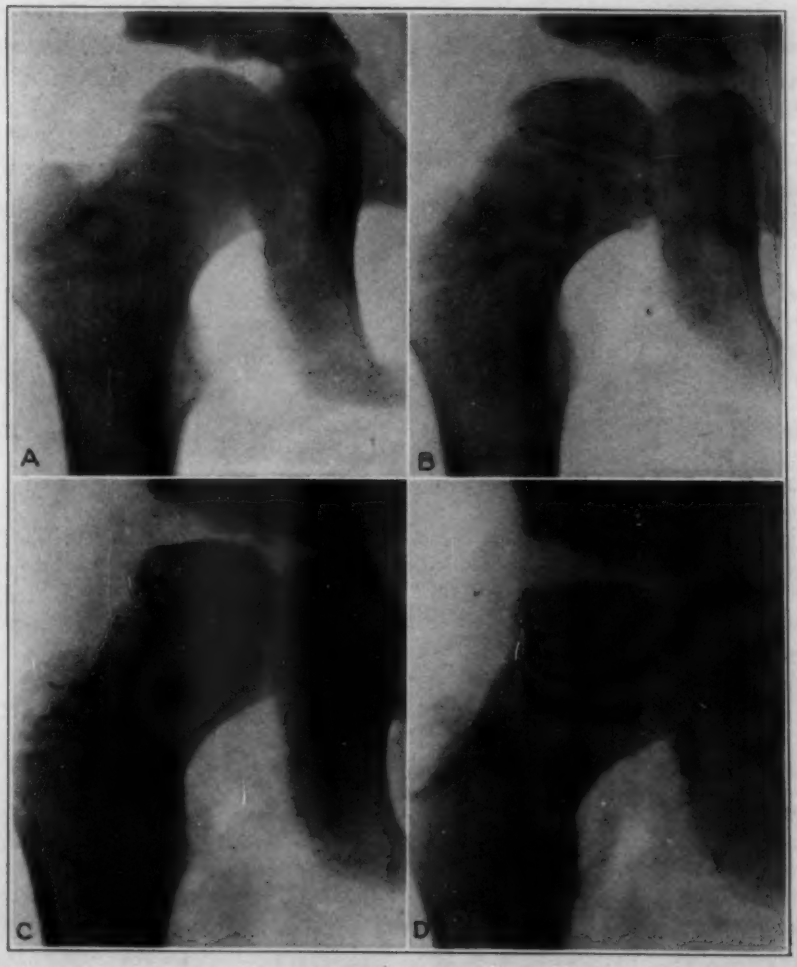

Fig. 1.—*A* shows the taller outer portion of the bony nucleus of the capital epiphysis. *B* discloses slight flattening of the outer portion of the bony nucleus of the capital epiphysis in a boy of 6 years with Perthes' disease in an early stage. Motion in the affected hip is limited. *C* shows definite flattening of the outer portion of the bony nucleus of the capital epiphysis in a boy of 7 years with early Perthes' disease. *D*, taken three months later than *C*, in the same case, shows accentuation of the flattening and an area of cystic rarefaction in the metaphysis.

outer portion of the capital epiphysis (fig. 1 *B*). Concomitantly there is a slight increase in the joint space.[1] This is not the result of separation or dislocation of the femur from the acetabulum. It seems fair to reason by inference that it is due to resorption of the bone with replacement by soft tissue.[2]

In addition, the density of the capital head, as determined by roentgenogram, may also become modified. However, the density of the region in question may appear normal. This shadow, nevertheless, may be slightly more opaque than the atrophic metaphysial region of the involved femur. It seems to us that the normal density of the

1. The joint space as observed on the roentgenogram is the distance between the subchondral zone (provisional zone of calcification) of the femoral capital epiphysis and that of the roof of the acetabulum.

2. Perthes, G.: Ueber Osteochondritis deformans juvenilis, Arch. f. klin. Chir. **101**:779, 1913. Legg, A. T.: Osteochondral Trophopathy of the Hip-Joint, Surg., Gynec. & Obst. **22**:307, 1916. Sundt, H.: Malum Coxae Calve-Legg-Perthes, Zentralbl. f. Chir. **47**:538, 1920. Sorrel, E.: Six cas d'ostéo-chondrite déformante infantile de l'épiphyse fémorale supérieure, Rev. d'orthop. **8**:31, 1921. Kreuter, E.: Zur Aetiologie und Pathogenese der Osteochondritis deformans juvenilis (Perthes), Beitr. z. klin. Chir. **122**:263, 1921. Waldenstrom, H.: The Definite Form of Coxa Plana, Acta radiol. **1**:384, 1922. Vignard: Deux biopsies dans 2 cas d'ostéo-chondrite déformante juvenile, Arch. franco-belges de chir. **25**:1088, 1922. Heitzmann, O., and Engel, H.: Epiphysenerkrankungen in Wachstumsalter, Klin. Wchnschr. **2**:397 (Feb.) 1923. Jansen, M.: Coxa Plana and Its Causation, J. Bone & Joint Surg. **5**:265 (April) 1923. Kirklin, B. R.: Osteochondritis Deformans Juvenilis, Am. J. Roentgenol. **10**:701 (Sept.) 1923. McWhorter, G. L.: Operation on Neck of Femur Following Acute Symptoms in a Case of Osteochondritis Deformans Junvenilis Coxae (Perthes' Disease), Surg., Gynec. & Obst. **38**:632 (May) 1924. Walter, H.: Zur Histologie der Perthes'schen Krankheit, München. med. Wchnschr. **72**:499 (March) 1925. Moller, P. F.: Clinical Observations After Healing of Calve-Perthes' Disease Compared with Final Deformities Left by That Disease and the Bearing of Those Final Deformities on Ultimate Prognosis, Acta radiol. **5**:1, 1926. Legg, A. T.: The End Results of Coxa Plana, J. Bone & Joint Surg. **9**:26 (Jan.) 1927. Rockemer, K.: Zur Histopathogenese der Perthesschen Krankheit, an der Hand eines Frühfalles, Frankfurt. Ztschr. f. Path. **35**:1, 1927. Zemansky, A. P., Jr.: Pathology and Pathogenesis of Legg-Calve-Perthes' Disease, Am. J. Surg. **4**:169, 1928. Lippmann, R. K.: The Pathogenesis of Legg-Calvé-Perthes' Disease Based upon the Pathologic Findings in a Case, ibid. **6**:785 (June) 1929. Freund, E.: Zur Deutung des Röntgenbildes der Perthesschen Krankheit, Fortschr. a. d. Geb. d. Röntgenstrahlen **42**:435 (Oct.) 1930. Lang, F. J.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, J. Bone & Joint Surg. **14**: 563 (July) 1932. Cage, H. C.: A Possible Early Sign of Perthes' Disease, Brit. J. Radiol. **6**:295 (May) 1933. Freund, E.: Active and Passive Pleat Formation of Joint Cartilage, Arch. Path. **18**:186 (Aug.) 1934. King, E. S. J.: Localized Rarefying Conditions of Bone, Baltimore, William Wood & Company, 1935. Brailsford, J. F.: The Radiology of Bones and Joints, Baltimore, William Wood & Company, 1935. Eyre-Brook, A. L.: Osteochondritis Deformans Coxae Juvenilis or Perthes' Disease, Brit. J. Surg. **24**:166 (July) 1936.

capital epiphysis may reflect either partially or totally necrotic bone. We do know that unresorbed necrotic bone may give a normal roentgenographic picture.[3]

However, at varying intervals from the incipiency of symptoms the roentgenographic density of part or most of the head may alter. The shadow cast may appear similar to that of dense sclerotic bone. In one particular instance this was observed after two months (fig. 2). Exaggerated opacity of this region is probably dependent on the presence of newly formed living bone about, and the partial compression of, the original necrotic bone trabeculae. When these two conditions are absent, the density of the shadow is normal.

Fig. 2.—*A* shows early changes of Perthes' disease in a boy of 5 years; *B*, the increasing density of the femoral head two months later.

It is of interest to mention here that specimens of the femoral head removed because of nonunion of the fractured femoral neck, in adults, showed on histologic and roentgenologic examination that when new bone formed about the original unresorbed necrotic trabeculae the roentgenographic picture displayed an absolute increase in the density (opacity) of the femoral head. However, should the process of resorption of the original bone keep pace with new bone formation, absolute sclerosis as evidenced roentgenographically may not appear. On the same basis, if resorption continues without the building of new bone, rarefaction (atrophy) will be observed on the roentgenographic film. Sclerosis should in any case not be considered the result only of

3. Jaffe, H. L., and Pomeranz, M. M.: Changes in Bones of Extremities Amputated Because of Arteriovascular Disease, Arch. Surg. **29**:566 (Oct.) 1934.

mechanical compression of the trabeculae. Actual compression of trabeculae has, however, been observed microscopically in cases of severe osteoporosis, in cases of long-standing arthritis with secondary subchondral cyst formation and in cases of slipping of the capital epiphysis.

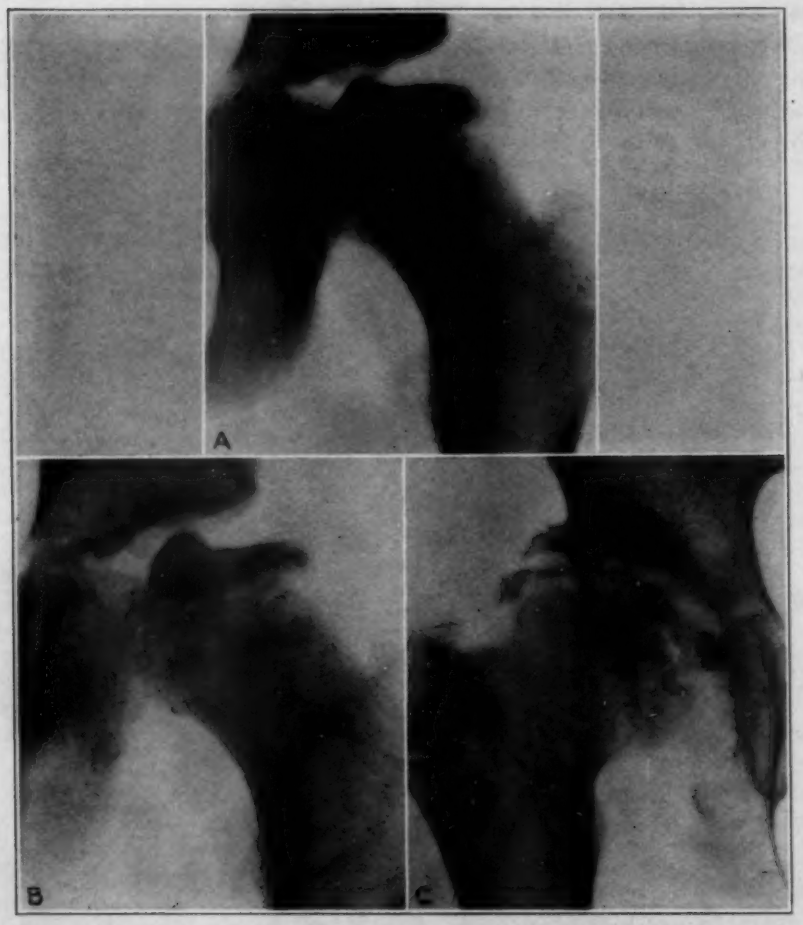

Fig. 3.—*A* shows extreme sclerosis of the femoral head and resorption of the outer portion. *B*, which presents a later stage of the condition shown in *A*, reveals rarefaction of the metaphysial zone. *C*, taken in another case, shows extreme flattening and irregularity of the bony portion of the femoral epiphysis.

With active resorption of the original femoral epiphysis, the roentgenogram may exhibit constant gradual diminution in the shadow representing the bony elements (fig. 3). In addition, the film may disclose islands of sclerotic bone with neighboring areas of rarefied

bone or no bone (fragmentation, fig. 4). This appearance has been caused probably by local variations in the degree of resorption and production of bone. Occasionally the films present relatively opaque shadows of triangular-shaped pieces of bone (sequestrums?) located approximately in the region where the ligamentum teres inserts into the femoral head (fig. 5). Such areas of increased density may be the result of production of new bone and of compression of some of the original trabeculae. The round ligament may provide enough blood channels to induce building of new bone.

In roentgenograms, even in many of those made soon after the onset of symptoms, bone can be seen extending from the femoral capital epiphysis laterally beyond the limits of the roof of the acetabulum. It

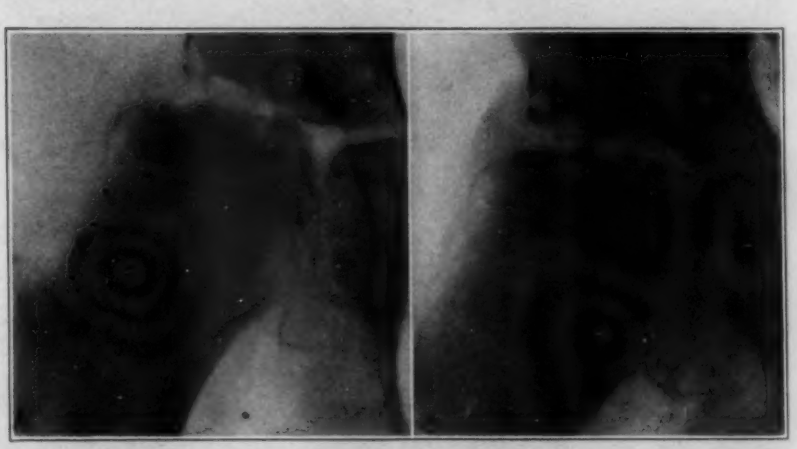

Fig. 4.—*A* shows a shadow appearing as an island of dense bone. *B*, taken three months later, shows diminution in the density of this shadow following the application of a plaster of paris spica. Note the irregularities in the contour of the acetabular roof.

may appear as a ledge of bone extending over the metaphysis (fig. 5). Usually the bone in question is not sclerotic. It is more than likely that it has not formed in consequence of mechanical compression, i. e., extrusion. It is known that, especially in the young, there is good blood supply in the region where the periosteum of the femoral neck meets the articular cartilage. Here, also, osteogenesis may be provoked by abnormal irritation of the tissue. It is probably in this area that new bone forms in conjunction with either rarefaction or condensation of the outer portions of the capital epiphysis.

With progressive resorption, the femoral epiphysis may be so reduced as to appear wafer-like roentgenographically. In a few cases we noted that practically all the bone was resorbed. In the majority

of instances the width of the translucent zone (joint space) appeared increased. The greater trochanter of the involved femur may be at the same height as its mate or it may be a trifle higher if adduction of the involved femur is absent. This indicates further that the translucent zone (joint space) may be occupied by soft tissue. In two cases

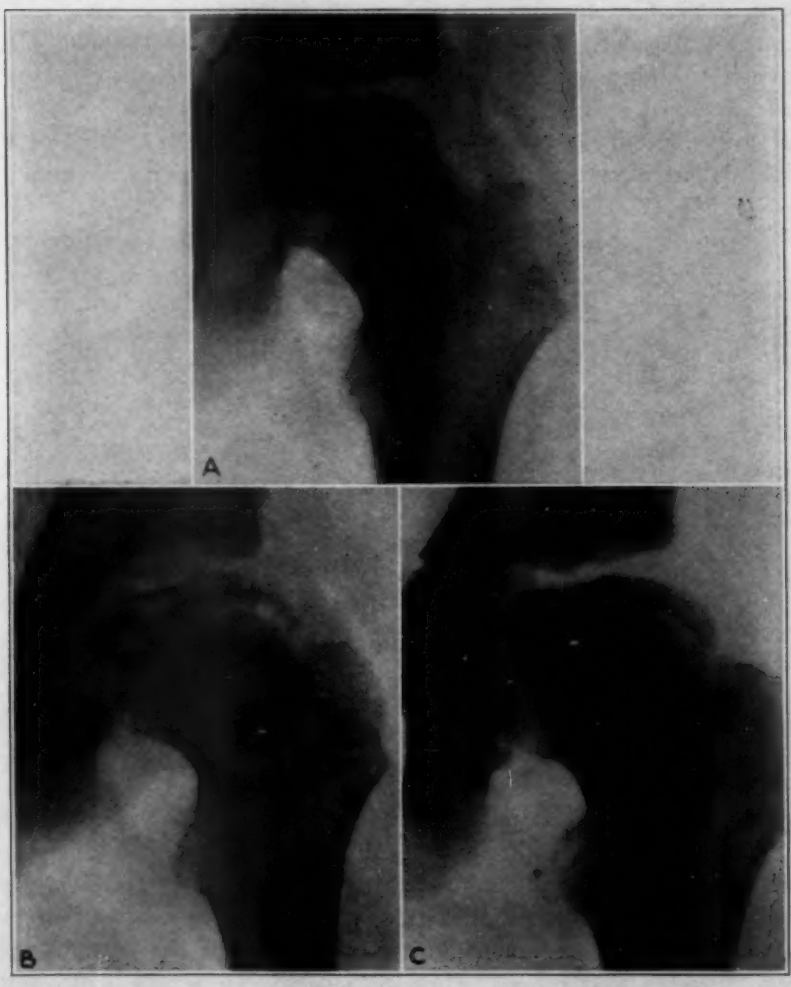

Fig. 5.—*A* reveals a sclerotic zone in the femoral epiphysis of a 6 year old girl. She had limped for four months. Note the flattening of the femoral epiphysis and the "beaking" of the outer portion. *B*, taken four months later, shows almost complete disappearance (resorption) of the sclerotic zone. Note the flattening of the caput and the pronounced "beaking" of the outer portion. *C*, taken eight months later than *B*, reveals increasing sclerosis of the femoral head (healing), "beaking" of the femoral head and widening of the femoral neck. Note that the neck appears short, but that this is not a coxa vara deformity.

in our series the width of the translucent zone was less than normal; the greater trochanter was elevated above its normal site, causing an actual shortening of the limb.

The changes described do not reach the same proportion in all cases, nor is there any regularity in their progression. In some the resorptive phenomena may be mild; in others, quite severe. There is no definite

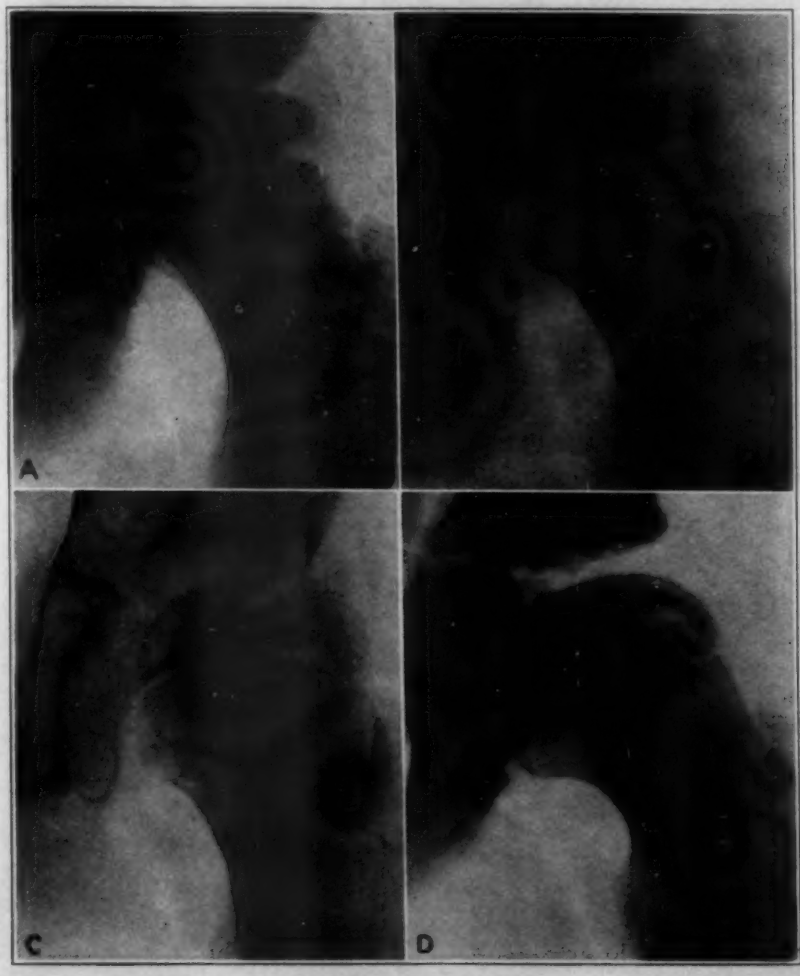

Fig. 6.—*A* shows early changes of Perthes' disease in a boy 7½ years old. Note the sclerosis and flattening of the head. *B*, taken after six months of immobilization, shows a diminution of the area of sclerosis. *C*, taken nine months after *B*, exhibits almost complete disappearance of the sclerosis in the femoral head. *D* shows the end-result in another case after immobilization of the hip in a brace for eighteen months. Note the smooth contour and uniform sclerosis of the femoral head.

plan, and there are minor variations. Each patient has his own characteristic transformations. In those in whom bone dissolution is at a minimum and the shape of the epiphysis has not been markedly remodeled, the sclerosis of the head may disappear in from six to eighteen months (fig. 6 *A*, *B* and *C*). In some cases complete transformation of the pathologic head to one with some semblance of nor-

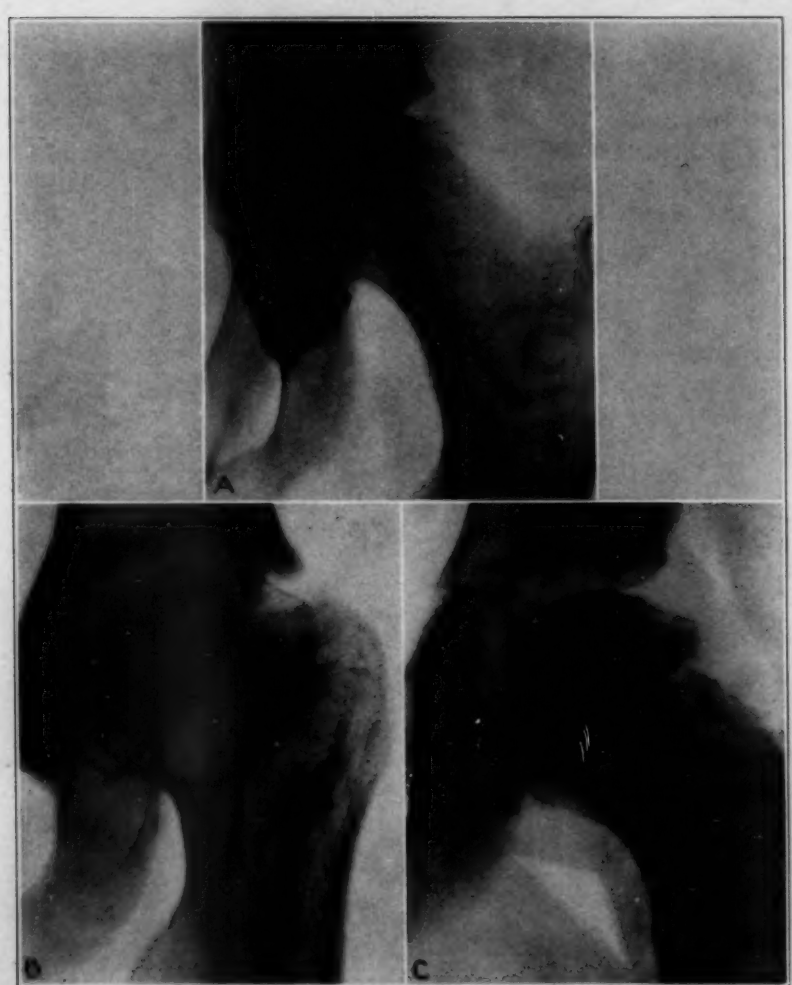

Fig. 7.—*A* shows the hip of a patient with Perthes' disease, taken six months after the onset of symptoms. *B*, taken seven years after *A*, reveals secondary hypertrophic osteo-arthritis. Note the enlargement of the femoral head, the narrowing of the joint space, the rarefactions in the femoral head and the shortening of the femoral neck. *C* shows the hip of another patient. Note in particular a defined area of rarefaction in the metaphysis.

mality has been observed to occur within sixteen months; in others, the period has varied from one to four years (fig. 6 *D*). Usually, the affected femoral head is wider, owing to the amalgamation of the bone previously formed in the outer portion of the femoral head with that of the epiphysis. Part of the head may extend over the femoral neck and almost reach the tip of the greater trochanter. The flattened femoral epiphysis may also be restored approximately to its normal height.

In most instances, the femoral head even years after the onset of Perthes' disease contains areas of bone of different densities. This indicates probably incomplete realinement and transformation of the old and newly formed bone. There may be roentgenographic evidence of arthritis with single or multiple subchondral cysts. This is often seen in adults who have had either recognized or unrecognized symtoms and signs of Perthes' disease (fig. 7 *A* and *B*).

2. *Changes in the Femoral Neck.*—With the early alterations in the femoral capital epiphysis, there may be concomitant generalized rarefaction or atrophy of the metaphysial zone. This is usually the result of disuse. The region of the epiphysial cartilage plate may also lose its normal opacity. In some, instead of generalized atrophy, clear-cut single or multiple areas of rarefaction are seen just beneath the region of the epiphysial cartilage (fig. 7 *C*). They may make their appearance early in the disease or several months after the onset. These cystlike shadows may at a later date be lined or delimited by dense bone trabeculae (fig. 8). Even in patients showing healing or formation of new bone in the femoral capital epiphysis such rarefactions in the femoral neck demarcated by thick trabeculae were observed. Some were situated from 0.5 to 1.5 cm. distal to the epiphysial cartilage plate. These cystlike spaces may have the roentgenographic appearance of abscess cavities.

The cystic spaces in the femoral neck are not the result solely of atrophy from disuse. These changes most likely represent local cessation of endochondral ossification of the epiphysial cartilage plate plus resorption of the existing bone trabeculae. Fibrous tissue invasion of the cartilage plate of the metaphysis is the causative factor of the alterations.[4] Involvement of the epiphysial cartilage plate in the early years of life may result in a coxa vara deformity.

4. Delitala, E.: Contribution for the Study of a Typical Disease of the Upper End of the Femur (Perthes' Disease), Am. J. Orthop. Surg. **12**:555 (April) 1915. Lang, F. J.: Mikroskopische Befunde bei juveniler Arthritis deformans nebst vergleichenden Untersuchungen über die Femurkopfepiphyse mit besonderer Berücksichtigung der Fovea, Virchows Arch. f. path. Anat. **239**:76, 1922. Platt, H.: Pseudo-Coxalgia: A Clinical and Radiographic Study, Brit. J. Surg. **9**:366, 1922.

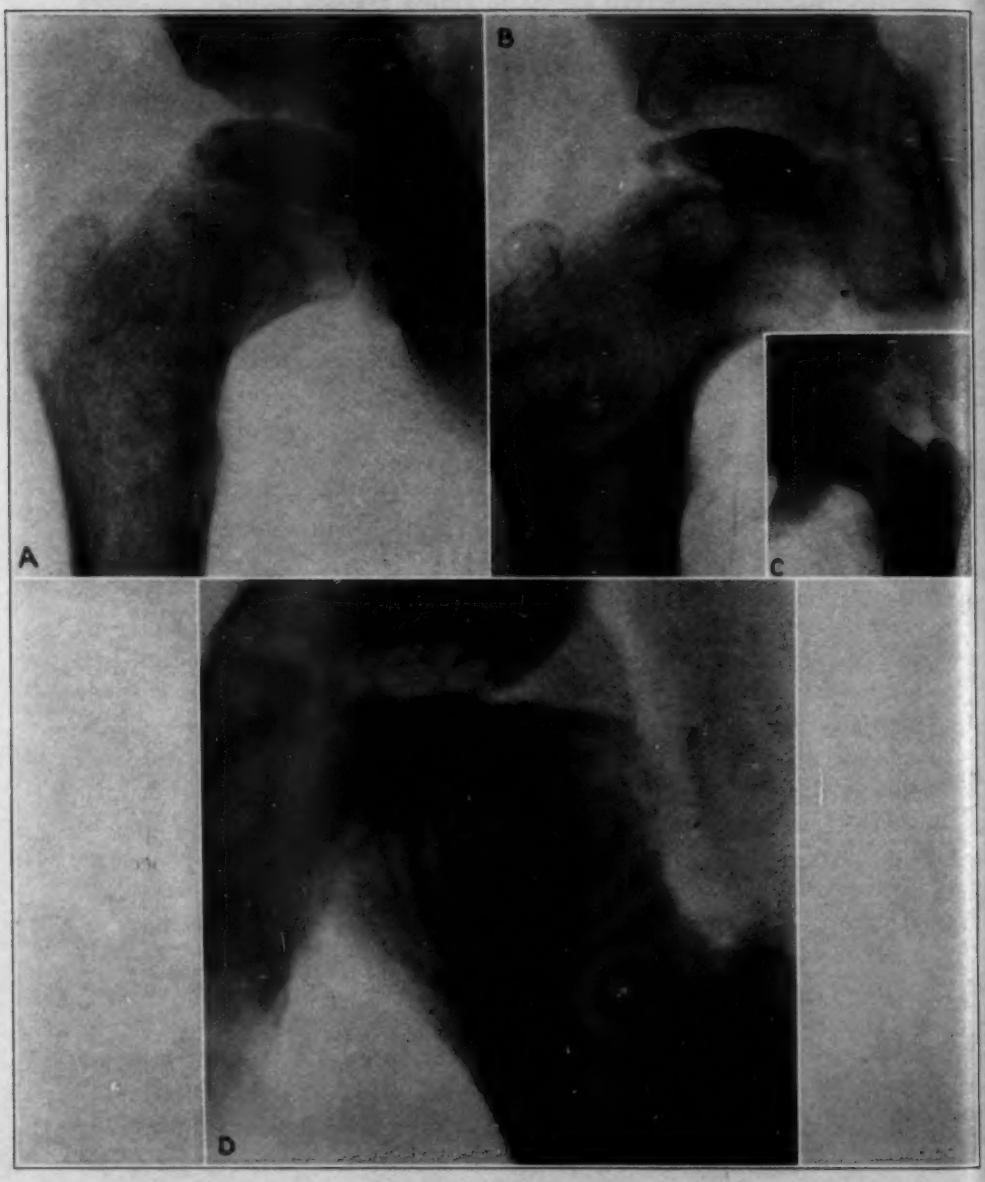

Fig. 8.—*A* (case of F. H., aged 6 years) reveals sclerosis of the flattened head and thickening of some of the trabeculae in the metaphysis. The latter condition produces a shadow resembling a cyst. The roentgenogram was taken thirteen weeks after the onset of symptoms. *B* (case of S. M., aged 6 years) shows a sclerotic flattened head and a cyst in the metaphysis. Compare with the normal mate (*C*). *D* (case of A. W.) reveals changes in the femoral head and circumscribed rarefied areas in the metaphysis.

In addition, the superior cortex of the femoral neck may also undergo pathologic transformation. This cortex (normally thinner than the inferior one) may become rarefied or may show evidences of periostitis (fig. 9*A*). When the femoral capital epiphysis widens and extends over the metaphysial zone, new bone forms on the superior cortex of the femoral neck in order to support this accessory portion of

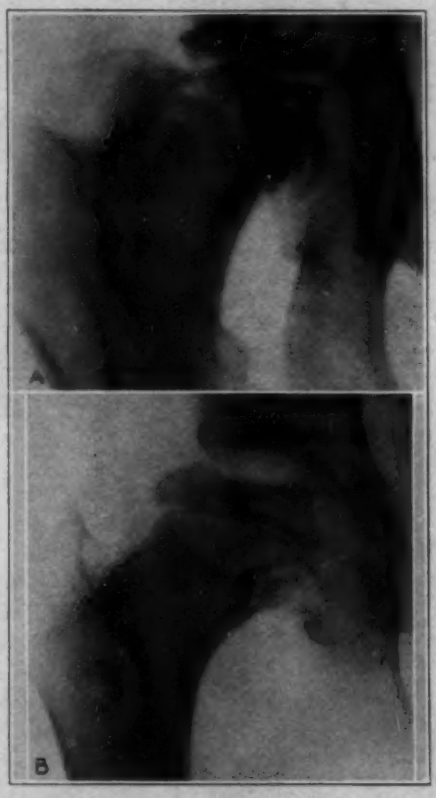

Fig. 9.—*A* (case of S. D., aged 12 years) shows irregularity in the contour of the femoral head, narrowing of the joint space and periostitis of the superior cortex of the neck. *B* (case of C. D., aged 10 years) exhibits changes in the caput and metaphysis. (The femur is in adduction and flexion.) There is an apparent increase in the joint space between the inner surface of the femoral head and the acetabulum.

the head. This accounts for the widening of the femoral neck as observed in Perthes' disease. (It is important to recognize that a normal femur in flexion or in external rotation may give a roentgenographic shadow which displays some widening and shortening of the femoral neck.)

Fig. 10.—*A* shows a case of Perthes' disease. *B* shows insertion of a hollow drill through the femoral neck and part of the head. *C*, taken four months after drilling, discloses the channel formed by the drill. *D*, taken two and one-half years after drilling, reveals especially the foreshortened femoral neck.

3. *Changes in the Acetabulum.*—Because of the deformity in one hip, there exists usually asymmetry of the right and left halves of the pelvic bones. This was recognized on the roentgenogram by the inequality in size of the obturator foraminae. Consequently, the roentgenogram of the involved limb showed in many cases irregularity in the configuration of the "tear drop." There was also an appearance of flaring of the inner acetabular wall (fig. 9*B*). In addition, on the

Fig. 11.—Reduced congenital dislocation of left hip. Note the contour of the left femoral head and the irregular configuration of the roof of the left acetabulum.

affected side the distance between the medial surface of the involved femoral head (even when an adduction deformity was absent) and the inner acetabular wall was increased. In a few patients, atrophy of the roof of the acetabulum, and in older ones, sclerosis, was observed. In several, irregularities in the contour of the extreme tip of the roof of the acetabulum (spur formation) were encountered, while in still others the inner acetabular wall was irregular and flared medially.

SUMMARY AND CONCLUSIONS

An analysis was made in an attempt to interpret the roentgenographic appearances observed in Perthes' disease in the light of modern pathology. Of special interest were the discrete pseudocystic areas in the femoral neck. These were believed to have resulted from, or been directly caused by, fibrous invasion or temporary cessation of growth of part, or of the whole, of the epiphysial cartilage plate. Interference with the growth of this plate can also follow surgical intervention, such as drilling or pegging of the femoral neck (fig. 10).

In this study we noted that reduced congenital dislocation of the hip as well as healed syphilitic osteochondritis or Morquio's disease may in certain cases at first hand simulate Perthes' disease roentgenographically (fig. 11). However, we observed in several cases of the first-named condition that the entire femoral capital epiphysis was usually flattened, with the medial half involved to a greater degree (the reverse of Perthes' disease).[5] In the cases of syphilitic osteochondritis and of Morquio's disease concomitant lesions existed in other bones.

As for the etiology of Perthes' disease, the roentgenographic and pathologic observations shed little light. However, the changes observed in the femoral epiphysis and metaphysis may to a certain degree be comparable to those occurring in bones involved by acute traumatic necrosis—for example, those following sprains of the knee, ankle, elbow or wrist.

Dr. H. L. Jaffe gave many helpful criticisms.

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5. Mayr, O.: Ueber Ossifikationsstörungen vor und wahrend der Luxationsbehandlung, Ztschr. f. orthop. Chir. **61**:66, 1934. Marottole, O.: Malattia di Perthes e sublussazione congenita dell'anca, Chir. d. org. di movimento **20**:161, 1934.